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DRAFT

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Title Page

Draft Report for Task Order No. UIC-24

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

Sponsor: U.S. Army Medical Materiel Development Activity

Test Article: WR6026 Dihydrochloride

Contract No.: DAMD17-92-C-2001

Study Director

Debra L. Kirchner, Ph.D., D.A.B.T.

In-Life Phase Completed On

September 9, 1996

Performing Laboratory

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This study evaluated the toxic potential of WR6026 Dihydrochloride on reproductive capability in CD® male and female rats. WR6026 Dihydrochloride is being developed as an antileishmanial agent. Doses of 0, 3.0, 7.5, and 18 mg base/kg/day were selected on the basis of dose range-finding and developmental toxicity studies in female rats (UIC/TRL Study Nos. 170 and 171, respectively) and a three month toxicity study with a three month recovery period in male and female rats (UIC/TRL Study No. 091). In the present study, doses of 0, 3.0, 7.5, and 18 mg base/kg/day were administered by daily gavage to male CD® rats for at least 54 days and to pregnant female CD® rats for 22 - 26 days in sperm-positive animals and for 33 days in sperm-negative females subsequently palpated pregnant. This included 29 days of dosing prior to cohabitation in males and 15 days of dosing prior to cohabitation in females. One mid dose female was found dead on precohabitation day 13 in the absence of clinical signs and necropsy observations. No mortalities occurred in the high dose. Toxicity occurred in males at 18 mg base/kg/day and in females at 7.5 and 18 mg base/kg/day. Cyanosis seen as blue tongue was observed in both sexes at the high dose. Significantly reduced food consumption and body weights were noted in males at 18 mg base/kg/day essentially throughout the entire study. Decreased organ to brain weight ratios were noted in high and mid dose males for the epididymis. There were no treatment-related effects on sperm motility, count, or morphology in any WR6026 Dihydrochloride-treated group, and no apparent effect on the males' ability to impregnate the females. Females at 7.5 and 18 mg base/kg/day had significant reductions in food consumption and body weight gains during the precohabitation phase. Significantly reduced body weights continued during the gestation phase in females at the high dose. At 18 mg base/kg/day, insignificantly reduced numbers of *corpora lutea* occurred concomitant with significantly decreased numbers of implantations and viable fetuses. There were no effects on estrus cycle parameters in any group; mating and fertility were also unaffected by treatment with WR6026 Dihydrochloride at any dose level. This suggests that administration of 18 mg base/kg/day of WR6026 Dihydrochloride for 15 days prior to mating affected oocyte maturation but not ovulation, mating behavior, implantation, or embryonic development. The no-observable-effect level (NOEL) for reproductive capability of males was 18 mg base/kg/day in spite of toxicity observed at this dose level. Based on the findings of altered maturation of oocytes at the high dose, the NOEL for females was 7.5 mg base/kg/day even though mating and fertility were unaffected at any dose level.

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Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-24
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STATEMENT OF COMPLIANCE

Study No. 218 entitled "Oral Fertility and Early Embryonic Development Study of WR6026 Dihydrochloride in Rats" was conducted in compliance with the Good Laboratory Practices regulations as published in 21 CFR 58, 40 CFR 160 and 40 CFR 792 in all material aspects.

The protocol for this study was approved by the UIC Animal Care Committee.

Signature

Study Director

_____ _____

Debra L. Kirchner, Ph.D., D.A.B.T. Date

DRAFT

QUALITY ASSURANCE STATEMENT

STUDY TITLE: ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

STUDY NUMBER: 218

STUDY DIRECTOR: DEBRA L. KIRCHNER

INITIATION DATE: 5/9/96

This study has been divided into a series of phases. Using a random sampling approach, Quality Assurance personnel monitors each of these phases over a series of studies. Procedures, equipment, documentation, etc., are examined in order to assure that the study is performed in accordance with the Good Laboratory Practice regulations of the Food and Drug Administration and the Environmental Protection Agency to assure that the study is conducted according to the protocol.

The following are the inspection dates, phases inspected, and report dates of QA inspections of the study.

INSPECT ON 5/9/96, TO STUDY DIR 5/9/96, TO MGMT 5/9/96
PHASES: PROTOCOL REVIEW

INSPECT ON 7/23/96, TO STUDY DIR 7/24/96, TO MGMT 7/25/96
PHASES: ANIMAL IDENTIFICATION, BODY WEIGHT, FOOD CONSUMPTION AND RANDOMIZATION

INSPECT ON 8/8/96, TO STUDY DIR 8/8/96, TO MGMT 8/12/96
PHASES: TEST ARTICLE ANALYSIS

INSPECT ON 8/9/96, TO STUDY DIR 8/12/96, TO MGMT 8/13/96
PHASES: ANIMAL IDENTIFICATION AND BREEDING

INSPECT ON 8/26/96, TO STUDY DIR 8/26/96, TO MGMT 9/3/96
PHASES: ANIMAL IDENTIFICATION, EUTHANASIA AND NECROPSY

INSPECT ON 10/29-30/96, TO STUDY DIR 10/30/96 TO MGMT 11/4/96
PHASES: RAW DATA

INSPECT ON 11/14-15/96, TO STUDY DIR 11/15/96, TO MGMT 11/15/96
PHASES: RAW DATA AND DRAFT REPORT FROM THE ANALYTICAL LAB

INSPECT ON 12/3-4/96, TO STUDY DIR 12/4/96, TO MGMT 12/4/96
PHASES: MALE REPRODUCTIVE ASSESSMENT REPORT

INSPECT ON 12/17-18/96, TO STUDY DIR 12/18/96, TO MGMT 12/19/96
PHASES: DRAFT REPORT

Ronald Schlenbuck 12/19/96

QUALITY ASSURANCE DATE

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Signature Page

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT
STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

Sponsor: U.S. Army Medical Materiel
Development Activity
Fort Detrick
Frederick, MD 21702-5009

Test Article: WR6026 Dihydrochloride

Sponsor
Representative: George J. Schieferstein, Ph.D.

Testing Facility: TOXICOLOGY RESEARCH LABORATORY (TRL)
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Debra L. Kirchner, Ph.D., D.A.B.T. Date
Study Director

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Barry S. Levine, D.Sc., D.A.B.T. Date
Principal Investigator

Study Initiation: May 9, 1996

Dosing Initiation: July 12, 1996

In-Life Completion: September 9, 1996

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APPENDICES

1. SUMMARY

This study evaluated the toxic potential of WR6026 Dihydrochloride on reproductive capability in CD® male and female rats. WR6026 Dihydrochloride is being developed as an antileishmanial agent. Doses of 0, 3.0, 7.5, and 18 mg base/kg/day were selected on the basis of dose range-finding and developmental toxicity studies in female rats (UIC/TRL Study Nos. 170 and 171, respectively) and a three month toxicity study with a three month recovery period in male and female rats (UIC/TRL Study No. 091).

In the present study, doses of 0, 3.0, 7.5, and 18 mg base/kg/day were administered by daily gavage to male CD® rats for at least 54 days and to pregnant female CD® rats for 22 - 26 days in sperm-positive animals and for 33 days in sperm-negative females subsequently palpated pregnant. This included 29 days of dosing prior to cohabitation in males and 15 days of dosing prior to cohabitation in females. The results are summarized in Table 1.

One mid dose female was found dead on precohabitation day 13 in the absence of clinical signs and necropsy observations. No mortalities occurred in the high dose. Toxicity occurred in males at 18 mg base/kg/day and in females at 7.5 and 18 mg base/kg/day. Cyanosis seen as blue tongue was observed in both sexes at the high dose. Significantly reduced food consumption and body weights were noted in males at 18 mg base/kg/day essentially throughout the entire study. Decreased organ to brain weight ratios were noted in high and mid dose males for the epididymis. There were no treatment-related effects on sperm motility, count, or morphology in any WR6026 Dihydrochloride-treated group, and no apparent effect on the males' ability to impregnate the females. Females at 7.5 and 18 mg base/kg/day had significant reductions in food consumption and body weight gains during the precohabitation phase. Significantly reduced body weights continued during the gestation phase in females at the high dose. At 18 mg base/kg/day, insignificantly reduced numbers of *corpora lutea* occurred concomitant with significantly decreased numbers of implantations and viable fetuses. There were no effects on estrus cycle parameters in any group; mating and fertility were also unaffected by treatment with WR6026 Dihydrochloride at any dose level. This suggests that administration of 18 mg base/kg/day of WR6026 Dihydrochloride for 15 days prior to mating affected oocyte maturation but not ovulation, mating behavior, implantation, or embryonic development. The no-observable-effect level (NOEL) for reproductive capability of males was 18 mg base/kg/day in spite of toxicity observed at this dose level. Based on the findings of altered maturation of oocytes at the high dose, the NOEL for females was 7.5 mg base/kg/day even though mating and fertility were unaffected at any dose level.

2. INTRODUCTION

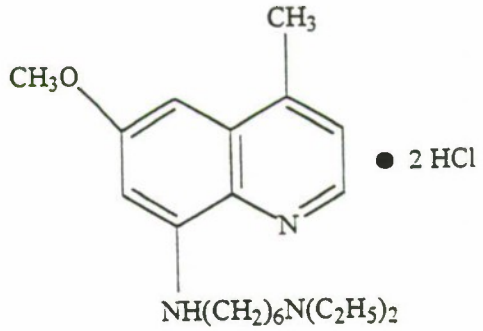
This study was conducted to evaluate the toxic potential of WR6026 Dihydrochloride on the reproductive capability of male and female rats. WR6026 Dihydrochloride is being developed as an antileishmanial agent. The test article was administered by daily gavage to male CD® rats for at least 54 days and to pregnant CD® rats for 22 - 26 days in sperm-positive females and for 33 days in sperm-negative females subsequently palpated pregnant. This included 29 days of dosing prior to cohabitation in males and 15 days of dosing prior to cohabitation in females. All methods and procedures were conducted in accordance with the Toxicology Research Laboratory,

University of Illinois at Chicago and Pathology Associates, Intl. Quality Assurance Programs designed to conform with FDA Good Laboratory Practices Regulations. No unforeseen circumstances affected the integrity of the study. This study was initiated on May 9, 1996; dosing began July 12, 1996 (males) and July 26, 1996 (females). The in-life portion was terminated on September 9, 1996 (last female necropsy).

3. MATERIALS AND METHODS

3.1 Test Article

WR6026 Dihydrochloride (Bottle No. BK01845), a light yellow powder, was provided by the Sponsor and was received on June 4, 1996, from Herner and Co., Rockville, MD. The test article was previously assigned an in-house chemical number (1540614). The chemical name of the test article is 6-Methoxy-8-(6-diethylaminohexylamino) lepidine dihydrochloride and the mole fraction of the base is 0.825. It was stored at -15° to -20°C in an amber bottle. The chemical structure follows.



The Analytical Chemistry Report is contained in Appendix A. The test article was initially identified by GC-MS and the purity, as determined by HPLC, was 99.43 ± 0.3%. The terminal purity was 99.67 ± 0.04%. Thus, the test article was stable under storage conditions.

3.2 Animals

One hundred ten male and 120 female Virus Antibody Free (VAF) time-mated CD® rats were obtained from Charles River Breeding Laboratories, Portage, MI on June 26, 1996 and July 10, 1996, respectively. The animals were 8 weeks old upon arrival at the UIC AAALAC-accredited animal facility (male date of birth May 2, 1996; female date of birth May 15, 1996). Each animal was given a study-unique quarantine/pretest number as a subcutaneously implanted microchip. During randomization to treatment groups, each animal was re-assigned a unique animal number. The microchips were re-programmed and these latter animal numbers appeared on a cage card visible on the front of each cage. The cage card additionally contained the study number, test article identification, treatment group number, sex, and dose level. Cage cards were color-coded as a function of treatment group. Animals were singly housed in polycarbonate cages with Anderson

Bed-a-cob bedding (Heinold Co., Kankakee, IL) in a temperature (65 - 78°F) and humidity (30 - 70 %) controlled room with a 14 hour light/10 hour dark cycle. The cage size, 840 cm^2 area and 20 cm height, was adequate to house rats at the upper weight range as described in the *Guide for the Care and Use of Laboratory Animals*, National Research Council, 1996. All animals were routinely transferred to clean cages with fresh bedding weekly.

Certified Rodent Chow No. 5002 (PMI Feeds, Inc., St. Louis, MO) and tap water from an automatic watering system in which the room distribution lines were flushed daily were provided *ad libitum* from arrival until termination. The water was not treated with additional chlorine or HCl. There were no known contaminants in the feed or water which were expected to influence the study. The results of the most current comprehensive chemical analyses of Chicago water conducted by the City of Chicago are documented in files maintained by Quality Assurance.

3.3 Experimental Design

All animals were examined daily during the 15 day quarantine/pretest period, and were approved for use by the Clinical Veterinarian prior to being placed on study. Vaginal washings were performed in all females for 9 days during the quarantine/pretest phase in order to determine which females were cycling normally. Vaginal washings were also performed during the precohabitation phases to assess potential effects of treatment on the estrus cycle and during cohabitiation to detect positive evidence of mating. Near the end of the quarantine/pretest phase, 100 animals of each sex were randomized by sex into the four treatment groups as shown in the following table. The males and normally cycling females were randomized using a computer-generated randomization program, stratified on the basis of body weight.

Group	No. of Animals Male	Female	Treatment	Dose Level (mg base/kg/day)	Dose Conc. (mg base/ml)	Dose Volume (ml/kg/day)
1	25	25	Vehicle	0	0	5
2	25	25	WR6026 Dihydrochloride	3.0	0.6	5
3	25	25	WR6026 Dihydrochloride	7.5	1.5	5
4	25	25	WR6026 Dihydrochloride	18.0	3.6	5

Dose levels were selected on the basis of dose range-finding and developmental toxicity studies in female rats (UIC/TRL Study Nos. 170 and 171, respectively) and a three month toxicity study with a three month recovery period in male and female rats (UIC/TRL Study No. 091).

The gavage dosing procedure was accomplished by the use of a rigid oral feeding needle. Upon the recommendation of the clinical veterinarian, a rubber catheter was used for several days during the precohabitation phase to dose one control female (No. 617) which displayed dark red material around the eyes and nose as well as a mass on the left side (noted as an unscheduled clinical observation). All animals received the control article by gavage for the last three days during week -1 to acclimate them to the dosing procedure. The dosing suspensions were administered daily to male rats for 29 days prior to cohabitation, daily for 21 days until completion of the cohabitation phase, and for 4 - 6 days after completion of the cohabitation phase for a range of 54 - 56 dosing days. WR6026 Dihydrochloride was administered daily to females for 15 days prior to cohabitation, daily during their cohabitation phase, and daily during gestation days (GD) 0 to 6. GD0 was defined as the day sperm was observed in the vaginal washing, and females with a known GD0 were designated as sperm-positive. The majority of females became sperm-positive after 1 - 4 nights of cohabitiation. For these females, the overall dosing period was 22 - 26 days: 15 days during precohabitation, 0 - 4 days during cohabitation, and 7 days during gestation. Four females (two at 0, one at 7.5 and one at 18 mg base/kg/day) subsequently found to be pregnant did not have evidence of mating (i.e., sperm was not observed in the vaginal washing). These four animals were designated as sperm-negative. Since their GD0 was unknown, dosing and cohabitation of these females continued until pregnancy was subsequently confirmed by observation of a distended abdomen and/or palpation of fetuses *in utero*. The dosing period for these females was 33 days: 15 days during precohabitation and 18 days during cohabitation (i.e., until confirmation of pregnancy).

Test article dosing solutions were prepared weekly by dissolving the appropriate quantity of WR6026 Dihydrochloride (adjusted for purity) in the control article (deionized, distilled water). Each test article dosing solution was prepared individually by adding the appropriate amount of WR6026 Dihydrochloride with the required volume of control article in a pre-calibrated beaker. The contents were mixed with an Omni-Mixer homogenizer for at least 2 minutes. Stability data obtained from a previous study (UIC/TRL Study No. 091) indicated that dosing solutions of WR6026 Dihydrochloride were stable for at least 12 days. The dosing solutions (including controls) were stored at 2 - 8 °C and were allowed to warm to room temperature. Samples of all dosing solutions (including controls) were analyzed weekly prior to use and only solutions within 10% of their target concentration were used. Both the test article and control solutions were administered to the animals at a dosing volume of 5 ml/kg/day.

Body weights were recorded for all animals at randomization in week -1. For males, body weights were recorded twice weekly (every 3 - 4 days) during the dosing period. A final body weight was recorded on the day of scheduled necropsy. For females, body weights were recorded twice weekly (every 3 - 4 days) during the precohabitation and cohabitation dosing phases. Once evidence of positive mating was detected (i.e., sperm was observed in the vaginal washing), body weights for these sperm-positive females were obtained daily during the remainder of the dosing period, i.e., GD0 - 6, and then in the postdosing period on GD10, 13, and 16. Food consumption for males was measured twice weekly (every 3 - 4 days) during week -1 and the dosing period except during cohabitation. Food consumption for females was measured twice weekly (every 3 - 4

days) during week -1 and precohabitation. Food consumption was not measured during cohabitation. When positive evidence of mating was detected (i.e., sperm in the vaginal washing), food consumption for females was measured during the following intervals: GD0 - 3; 3 - 6; 6 - 10; 10 - 13; and 13 - 16. All animals were observed daily for clinical signs of toxicity approximately 1 - 2 hours after dosing, and in the morning after completion of the dosing period for females. Animals were also observed twice daily (at least 6 hours apart) for moribundity/mortality.

One mid dose female (No. 660) was found dead prior to the start of the cohabitation phase on day 13. This animal was grossly examined externally and internally. No tissues were kept. Sperm-positive female rats were euthanized in random order by CO_2 asphyxiation on GD16. The four female rats (Nos. 605, 607, 674 and 688) that were sperm-negative but palpated pregnant were euthanized by CO_2 asphyxiation the day after pregnancy was confirmed (day 34, i.e., approximately 2 1/2 weeks after the initiation of cohabitation). Two female rats (Nos. 623 and 629) which were sperm-negative and not palpated pregnant were euthanized by CO_2 asphyxiation 10 days after the end of the cohabitation period (day 46). The necropsy for all females included opening the abdominal and thoracic cavities and grossly evaluating the viscera. The uterus and ovaries were removed from the body and examined. For gravid, sperm-positive animals, the number of *corpora lutea* on each ovary was recorded. Additionally, the number and location of implantation sites, viable and nonviable fetuses, and resorptions were recorded consecutively from the distal end of the left uterine horn to the cervix and then from the distal end of the right uterine horn to the cervix. The number of *corpora lutea* and implantation sites were also recorded for gravid, sperm-negative animals. A viable fetus was defined as one which had pink, well vascularized tissue; a dark red placenta; and clean, reddish amniotic fluid. A nonviable fetus was defined as one that had white, non-vascularized tissue; a necrotic, green placenta; and cloudy, dark amniotic fluid. Uteri from animals with no macroscopic evidence of implantations were opened and placed in 10% aqueous ammonium sulfide solution for approximately 10 minutes for detection of early embryolethality. Uteri and ovaries from all females and the mottled kidneys from dam Nos. 635 and 650 at 3 mg base/kg/day and from control dam No. 608 (for comparison) were retained in 10% neutral buffered formalin for possible histopathological evaluation. The Sponsor will provide written directions regarding the disposition of these tissues. Following gross necropsy examination, the carcass of each dam was discarded.

One mid dose male (No. 560), which was randomly assigned to the female which was found dead on day 13, was sacrificed on day 18 (i.e., 3 days after initiation of the cohabitiation phase) after confirmation that he was not needed for cohabitation with another mid dose female. This animal was grossly examined externally and internally. No tissues were kept. The remaining males were euthanized in random order by CO_2 asphyxiation on days 55 - 57 following a review and discussion with the Sponsor of the fertility and mating indices of the majority of females in all dose groups. The thoracic, abdominal, and pelvic cavities were opened and the viscera examined. Paired organ weights were collected from each animal for the testes, epididymides, and seminal vesicles. Prostate weights were also recorded, and brains were weighed for organ to brain weight ratio calculations. Both testes were retained in Bouin's fixative. The left

epididymis, prostate, and both seminal vesicles from all animals were retained in 10% neutral buffered formalin for possible histopathological evaluation. The Sponsor will provide written directions regarding the disposition of these tissues. The right epididymis was trimmed, frozen on dry ice, and temporarily stored at -70°C or less for subsequent sperm counts and sperm morphology assessment. Following gross necropsy examination, the carcass of each animal was discarded.

Sperm motility was assessed at the time of necropsy. Semen samples were evaluated utilizing the Hamilton Thorne Integrated Visual Optics System (IVOS) 10 Sperm Analyzer. The motility sample was prepared from the vas deferens and was placed in a suspension medium containing phosphate buffered saline (PBS) with 1% BSA (Bovine Serum Albumin). After a 3 minute swim out period, a 100 μ deep cannula was inserted into the media and a sample was drawn up. The cannula was inserted into the stage, and a general examination of the sperm sample was made on the computer monitor. Sperm samples were discarded after analysis.

Subsequent to the necropsy, the frozen epididymal samples were thawed, and the caudal section was weighed and minced. One or two drops of the sample was spread on a slide and stained with Eosin for sperm morphology assessment. The minced epididymal samples were homogenized, and a 100 μL sample was added to a vial containing a florescent dye which stained the DNA in the sperm head. A sample was loaded into the IVOS, and the stained sperm heads were counted. Results were reported as total sperm count adjusted for caudal epididymis weight (10^6 sperm/g tissue). Sperm samples were discarded after analysis.

3.4 Statistical Analyses

Body weights, body weight gains, calculated daily food consumption, male organ to brain weight ratios, the average number of occurrences of estrus, and the average length of the estrus cycle were analyzed by one-way analysis of variance. If a significant F ratio was obtained ($p \leq 0.05$), Dunnett's test was used for pair-wise comparisons to the vehicle control group.

Sperm counts, sperm morphology, and sperm motility; the numbers of *corpora lutea* (C.L.), implantations, resorptions, viable and nonviable fetuses; and the percent preimplantation loss*, postimplantation loss** and total implantation loss,*** were compared using the Kruskal-Wallis test. If a significant effect was seen ($p \leq 0.05$), the Mann-Whitney U test was used for pair-wise comparisons to the vehicle control group.

*Preimplantation loss% = [(#C.L. - #implantations)/# C.L.] x 100
**Postimplantation loss% = [(#implantations - #viable fetuses)/#implantations] x 100
***Total implantation loss% = [(#C.L. - #viable fetuses)/#C.L.] x 100

The number of females cycling normally and the following reproductive indices were analyzed by Fischer's exact test:

Mating Index = (No. with evidence of mating/No. cohoused) x 100
Fertility Index = (No. pregnant/No. with evidence of mating) x 100

Sperm-negative, pregnant animals were included in the analysis of the numbers of *corpora lutea* and implantations, the percent preimplantation loss, and the mating and fertility indices.

In addition to the written report, summary data tables of parameters and variability were transmitted to the Sponsor on magnetic media (computer diskette) in "ASCII" form. The transcribed data on disk are no longer considered GLP compliant.

4. RESULTS

4.1 Dosage Formulation Analyses

The results of dosage formulation analyses are shown in Table 2. The Analytical Chemistry Report is in Appendix A.

All dosage formulations used were within 10% of their respective target concentration prior to dosing.

4.2 Mortality/Clinical Signs

The summary of clinical signs are presented in Tables 3.1 and 3.2. Individual clinical signs are in Appendices B, D, and E.

4.2.1 Males

There was no mortality in male rats in any dose group. Sporadic occurrences of blue tongue were observed in 12/25 males at 18 mg base/kg/day. There were no clinical signs noted in any male at 3.0 or 7.5 mg base/kg/day.

4.2.2 Females

One female (No. 660) at 7.5 mg base/kg/day was found dead on precohabitation day 13. Prior to death, this animal exhibited reduced body weight gain and food consumption over the days 5 - 8 interval. There were no clinical observations prior to death, and the necropsy observations were unremarkable.

At 18 mg base/kg/day, clinical signs noted during the precohabitation and/or cohabitation phases were limited to sporadic occurrences of cyanosis seen as blue tongue in 15/25 animals. Sporadic occurrences of blue tongue were also noted in 10/24 females during the gestation phase. This included eight females that had displayed the sign in the precohabitation and/or cohabitation phase and two other females that had not previously displayed the sign. There were no mortalities in the 0, 3, or 18 mg base/kg/day groups, and no clinical signs occurred at 0, 3 or 7.5 mg base/kg/day.

4.3 Body Weights

The summaries of body weights and body weight gains are in Tables 4.1 - 4.3 and 5.1 - 5.3. Individual body weights and body weight gains are included in Appendices B, D, and E.

4.3.1 Males

In males at 18 mg base/kg/day, body weights were significantly reduced throughout the study (i.e., on days 5 - 54) which resulted in significantly reduced body weight gains noted for the intervals during days 0 - 5, 12 - 15, 19 - 22, and 40 - 43. These alterations contributed to a significant reduction in total body weight gain (≈ 25%). Significantly reduced body weight gains at 3.0 and 7.5 mg base/kg/day were noted during the days 0 - 5 interval, and were considered a response to initiation of test article administration. Body weight gains for the remainder of the study, as well as total body weight gains, and body weights were comparable to the controls.

4.3.2 Females

At 7.5 and 18 mg base/kg/day, steady but insignificantly reduced body weights noted on all precohabitation days. Consequently, slightly reduced body weight gains were noted at all intervals during the precohabitation phase and were significant during the interval over days 12 - 15 at the mid dose. These alterations contributed to a significant reduction in total body weight gains at 7.5 and 18 mg base/kg/day (35% and 45%, respectively). Administration of WR6026 dihydrochloride did not affect precohabitation body weight parameters at 3 mg base/kg/day.

At 18 mg base/kg/day, gestation body weights were significantly reduced on days 1 - 10; however, body weight gains were essentially comparable to the controls. A sporadic, but significant decrease in body weight gains over days 2 - 3 and a significant increase in body weight gains over days 10 - 13 were reflective of alterations observed in a few animals at each time-point. Administration of WR6026 Dihydrochloride did not affect gestation phase body weights at 3 and 7.5 mg base/kg/day.

4.4 Food Consumption

The summary of mean daily food consumption is presented in Tables 6.1 - 6.3. Individual food consumption data are shown in Appendix B, D, and E.

4.4.1 Males

At 18 mg base/kg/day, significantly reduced food consumption was observed essentially at all intervals throughout the study. Food consumption at 3 and 7.5 mg base/kg/day was

comparable to controls. Sporadic, but significant decreases noted over days 1 - 5 and 1 - 8 at 3 and 7.5 mg base/kg/day, respectively, were considered indicative of an initial response to administration of WR6026 Dihydrochloride.

4.4.2 Females

At 18 mg base/kg/day, significantly reduced food consumption occurred during the entire precohabitation phase (i.e., during the interval from days 1 - 15). Similarly, at 7.5 mg base/kg/day, significantly reduced food consumption occurred from precohabitation days 5 -15. These alterations continued into the gestation phase as significant reductions from days 0 - 10 at the high dose and from days 0 - 3 at the mid dose. Administration of WR6026 Dihydrochloride did not affect food consumption at 3 mg base/kg/day during any phase of the study.

4.5 Cesarean-Section Data

The summary of cesarean-section data is in Table 7. Individual animal data are presented in Appendix F.

At 18 mg base/kg/day, an insignificant reduction in the numbers of *corpora lutea* occurred with subsequent, significant reductions in the numbers of implantations and viable fetuses. The percent preimplantation loss, postimplantation loss, and total implantation loss were comparable to the controls. There were no effects of treatment on any evaluated parameter at 3 or 7.5 mg base/kg/day.

4.6 Female Reproductive Indices and Gross Necropsy Observations

The summary of female reproductive indices is presented in Table 8. The individual data including gross necropsy observations are shown in Appendix F.

Treatment with WR6026 Dihydrochloride had no effects on estrus cycling, mating, or fertility. Mottled kidneys noted in two females at 3 mg base/kg/day were considered incidental to treatment. No other gross lesions were observed at necropsy.

4.7 Male Reproductive Indices and Gross Necropsy Observations

The summary of male reproductive indices is in Table 9. The Sperm Analyses Report is in Appendix C.

There were no effects on sperm motility, count, or morphology in any WR6026 Dihydrochloride-treated group. At 18 and 7.5 mg base/kg/day, significant reductions were noted in organ to brain weight ratios for the epididymis. Prostate, seminal vesicles, and testes to brain weight ratios were unaffected by at least 54 days of treatment with 18 or 7.5 mg base/kg/day of WR6026 Dihydrochloride. Reproductive organ to brain weight ratios were not affected in the 3 mg base/kg/day group.

5. DISCUSSION

This study evaluated the toxic potential of WR6026 Dihydrochloride on reproductive capability in CD® male and female rats. Doses of 0, 3, 7.5, and 18.0 mg base/kg/day were administered by daily gavage to male CD® rats for at least 54 days and to pregnant female CD® rats for 22 - 26 days in sperm-positive animals and for 33 days in sperm-negative females subsequently palpated pregnant. This included 29 days of dosing prior to cohabitation in males and 15 days of dosing prior to cohabitation in females. The results are summarized in Table 1.

One mid dose female was found dead on precohabitation day 13 in the absence of clinical signs and necropsy observations. No mortalities occurred in the high dose. Toxicity occurred in males at 18 mg base/kg/day and in females at 7.5 and 18 mg base/kg/day. Cyanosis seen as blue tongue was observed in both sexes at the high dose. This finding was also noted in both sexes in the previously conducted thirteen week toxicity study with WR6026 Dihydrochloride. Significantly reduced food consumption and body weights were noted in males at 18 mg base/kg/day essentially throughout the entire study. Decreased organ to brain weight ratios were noted in high and mid dose males for the epididymis. Sperm is stored in this accessory organ where the process of maturation is completed (Eddy, 1988; Garside and Harvey, 1992; Thomas, 1991). Additionally, sperm also acquire fertilizing capability while in the epididymis. These events are dependent on hormone (testosterone, dihydrotestosterone, prolactin, and estrogen) and vitamins A and D which affect not only maturation but also transport of sperm through the epididymis. Levels of these hormones or vitamins were not ascertained in the this study. In spite of the reductions in epididymis to brain weight ratios as well as observations of toxicity in males at 18 mg base/kg/day, there were no treatment-related effects on sperm motility, count, or morphology in any WR6026 Dihydrochloride-treated group, and no apparent effect on the males' ability to impregnate the females.

Females at 7.5 and 18 mg base/kg/day had significant reductions in food consumption and body weight gains during the precohabitation phase. Significantly reduced body weights continued during the gestation phase in females at the high dose. At 18 mg base/kg/day, insignificantly reduced numbers of *corpora lutea* occurred concomitant with significantly decreased numbers of implantations and viable fetuses. There were no treatment-related alterations in the numbers of resorptions and nonviable fetuses, and the percent preimplantation and postimplantation losses were comparable between groups. Estrus cycle parameters and mating and fertility were also unaffected by treatment with WR6026 Dihydrochloride at any dose level. This suggests that administration of 18 mg base/kg/day of WR6026 Dihydrochloride for 15 days prior to mating affected oocyted maturation but not ovulation, mating behavior, implantation, or embryonic development. The NOEL for reproductive capability of males was 18 mg base/kg/day in spite of toxicity observed at this dose level. Based on the findings of altered maturation of oocytes, the NOEL for females was 7.5 mg base/kg/day even though mating and fertility indices were unaffected at any dose level.

6. REFERENCES

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7. PERSONNEL

Principal Investigator	Barry S. Levine, D.Sc., D.A.B.T.
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Report preparation was assisted by Ms. Soudabeh Soura, Ms. Nancy Dinger, and Mr. Mukesh Pitroda.

8. ARCHIVES

All raw data, documentation, specimens, test article reserves, and the final report are archived at the Toxicology Research Laboratory, University of Illinois at Chicago, Department of Pharmacology, 1940 W. Taylor St., Chicago, IL 60612-7353.

Table 1

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

Summary of Toxic Responses

Dose Level (mg base/kg/day)	0	3.0	7.5	18.0
Rats/Sex	25	25	25	25
Clinical Signs				
Males	-	NE	NE	BT(12)
Females: Precohabitation	-	NE	FD(1)	BT(15)
Gestation	-	NE	NE	BT(10)
Body Weight Gain: M/F	-	NE/NE	NE/↓	↓/↓
Food Consumption: M/F	-	NE/NE	NE/↓	↓/↓
Female Cesarean Section Evaluations				
No. *Corpora Lutea*	-	NE	NE	↓
No. Implantations	-	NE	NE	↓
No. Viable Fetuses	-	NE	NE	↓
Female Estrus Cycle Evaluations	-	NE	NE	NE
Mating and Fertility Indices	-	NE	NE	NE
Male Sperm Assessment	-	NE	NE	NE
Male Organ (% Brain Weight)	-	NE	↓EP	↓EP

CONCLUSIONS

This study evaluated the toxic potential of WR6026 Dihydrochloride on the reproductive capability of male and female CD®rats. Doses were 3.0,7.5, and 18.0 mg base/kg/day administered by daily gavage to male CD® rats for at least 54 days and to pregnant female CD® rats for 22 - 26 days in sperm-positive animals and for 33 days in sperm-negative animals subsequently palpated pregnant. This included 29 days of dosing prior to cohabitation in males and 15 days of dosing prior to cohabitation in females. One mid dose female was found dead on precohabitation day 13 in the absence of clinical signs and necropsy observations. No mortalities occurred in the high dose. Toxicity occurred in males at 18 mg base/kg/day and in females at 7.5 and 18 mg base/kg/day. Cyanosis seen as blue tongue was observed in both sexes at the high dose. Significantly reduced food consumption and body weights were noted in males at 18 mg base/kg/day essentially throughout the entire study. Decreased organ to brain weight ratios were noted in high and mid dose males for the epididymis. There were no treatment-related effects on sperm motility, count, or morphology in any WR6026 Dihydrochloride-treated group, and no apparent effect on the males' ability to impregnate the females. Females at 7.5 and 18 mg base/kg/day had significant reductions in food consumption and body weight gains during the precohabitation phase. Significantly reduced body weights continued during the gestation phase in females at the high dose. At 18 mg base/kg/day, insignificantly reduced numbers of *corpora lutea* occurred concomitant with significantly decreased numbers of implantations and viable fetuses. There were no effects on estrus cycle parameters in any group; mating and fertility were also unaffected by treatment with WR6026 Dihydrochloride at any dose level. This suggests that administration of 18 mg base/kg/day of WR6026 Dihydrochloride for 15 days prior to mating affected oocyte maturation but not ovulation, mating behavior, implantation, or embryonic development. The NOEL for reproductive capability of males was 18 mg base/kg/day in spite of toxicity observed at this dose level. Based on the findings of altered maturation of oocytes, the NOEL for females was 7.5 mg base/kg/day even though mating and fertility were unaffected at any dose level.

FD = Found Dead
NE = No Effect
↓ = Decreased
BT = Blue Tongue
EP = Epididymis

Table 2

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT
STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

Dosage Formulation Analyses[a]

Target Concentration	Week 1	% Target	Week 2	% Target	Week 3	% Target
0	0	-	0	-	0	-
0.6	0.579 ± 0.008	96.5	0.618 ± 0.021	103.0	0.587 ± 0.010	97.8
1.5	1.382 ± 0.013	92.1	1.500 ± 0.033	100.0	1.500 ± 0.035	100.0
3.6	3.526 ± 0.051	97.9	3.448 ± 0.037	95.8	3.417 ± 0.058	94.9

Target Concentration	Week 4	% Target	Week 5	% Target	Week 6	% Target
0	0	-	0	-	0	-
0.6	0.604 ± 0.001	100.7	0.604 ± 0.016	100.7	0.610 ± 0.008	101.7
1.5	1.523 ± 0.001	101.5	1.540 ± 0.006	102.7	1.387 ± 0.025	92.5
3.6	3.692 ± 0.011	102.6	3.626 ± 0.092	100.7	3.639 ± 0.051	101.1

Target Concentration	Week 7	% Target	Week 8	% Target
0	0	-	0	-
0.6	0.610 ± 0.001	101.7	0.600 ± 0.008	100.0
1.5	1.529 ± 0.001	101.9	1.428 ± 0.025	95.2
3.6	3.557 ± 0.053	98.8	3.495 ± 0.055	97.1

[a]Mean ± standard deviation for triplicate runs.

Table 3.1

DRAFT

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

SUMMARY OF CLINICAL SIGNS

STUDY: 218M SEX: MALE

DOSE: (mg base/kg/day)	0	3	7.5	18
GROUP:	1-M	2-M	3-M	4-M
Scheduled Sacrifice	25	25	24	25
Blue Tongue	0	0	0	12
Removed From Study	0	0	1[a]	0
Total Number of Animals	25	25	25	25

[a]One male at 7.5 mg base/kg/day was sacrificed on day 32 because the female with which he would have been paired was found dead on precohabitation day 13, and this male was not needed for any other mating pair in the mid dose group.

Table 3.2

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

SUMMARY OF CLINICAL SIGNS

STUDY: 218F SEX: FEMALE

DOSE: (mg base/kg/day)	0	3	7.5	18
GROUP:	1-F	2-F	3-F	4-F
PRECOHABITATION AND COHABITATION PHASES				
Animal Found Dead	0	0	1[a]	0
Dark Material Around Eyes	1	0	0	0
Dark Material Around Nose	1	0	0	0
Blue Tongue	0	0	0	15
Sacrificed	3[b,c]	1[c]	1[b]	1[b]
Total Number of Animals	25	25	25	25
GESTATION PHASE				
Scheduled Sacrifice[d]	22[e]	24	23[e]	24[e]
Blue Tongue	0	0	0	10

[a]One female at 7.5 mg base/kg/day was found dead on day 13.

[b]Two females at 0 mg base/kg/day and one female each at 7.5 and 18 mg base/kg/day did not have evidence of mating (i.e., sperm was not observed in the vaginal washing) but were palpated pregnant and sacrificed on day 34.

[c]One female each at 0 and 7.5 mg base/kg/day did not have evidence of mating (i.e., sperm was not observed in the vaginal washing) and were not palpated pregnant. These two animals were sacrificed on day 46.

[d]Only includes those animals with a known gestation day 0 (defined as the day sperm was observed in the vaginal washing). These animals were sacrificed on gestation day 16 except one female at 3 mg base/kg/day which was sacrificed on gestation day 17.

[e]Includes two females each at 0 and 18 mg base/kg/day and one female at 7.5 mg base/kg/day with a known gestation day 0 which were not pregnant when necropsied on gestation day 16.

Table 4.1

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

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SUMMARY OF BODY WEIGHTS (Grams)

STUDY: 218M SEX: MALE

PERIOD	DOSE: / GROUP:	0 1-M	3 2-M	7.5 3-M	18 4-M	(mg base/kg/day)
DAY -3	MEAN	346	346	346	346	
	S.D.	11.1	11.1	11.7	11.7	
	N	25	25	25	25	
DAY 1	MEAN	359	359	361	359	
	S.D.	12.2	13.2	12.7	14.3	
	N	25	25	25	25	
DAY 5	MEAN	379	373	373	365*	
	S.D.	15.3	14.7	13.6	16.9	
	N	25	25	25	25	
DAY 8	MEAN	392	385	386	376*	
	S.D.	16.9	16.9	14.5	18.2	
	N	25	25	25	25	
DAY 12	MEAN	406	401	402	387*	
	S.D.	20.7	19.2	16.4	23.1	
	N	25	25	25	25	
DAY 15	MEAN	417	410	413	389*	
	S.D.	21.3	21.5	18.1	28.9	
	N	25	25	25	25	
DAY 19	MEAN	433	422	428	399*	
	S.D.	24.0	30.3	21.3	28.1	
	N	25	25	25	25	
DAY 22	MEAN	444	435	439	405*	
	S.D.	25.4	24.9	22.3	29.1	
	N	25	25	25	25	
DAY 26	MEAN	459	453	455	420*	
	S.D.	27.3	26.0	26.7	29.9	
	N	25	25	25	25	
DAY 29	MEAN	461	456	455	422*	
	S.D.	27.0	27.4	31.2	31.0	
	N	25	25	25	25	

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

SUMMARY OF BODY WEIGHTS (Grams)

STUDY: 218M SEX: MALE

PERIOD	DOSE: GROUP:	0 1-M	3 2-M	7.5 3-M	18 4-M	(mg base/kg/day)
DAY 33	MEAN	471	465	465	433*	
	S.D.	28.0	26.6	28.8	31.0	
	N	25	25	24	25	
DAY 36	MEAN	480	474	475	441*	
	S.D.	28.4	28.9	29.6	32.3	
	N	25	25	24	25	
DAY 40	MEAN	495	491	492	457*	
	S.D.	31.0	29.4	32.7	33.3	
	N	25	25	24	25	
DAY 43	MEAN	504	498	499	462*	
	S.D.	32.0	30.7	33.1	35.4	
	N	25	25	24	25	
DAY 47	MEAN	519	511	513	476*	
	S.D.	33.8	32.1	36.6	37.3	
	N	25	25	24	25	
DAY 50	MEAN	526	518	518	482*	
	S.D.	35.3	32.5	36.3	37.0	
	N	25	25	24	25	
DAY 54	MEAN	534	527	528	490*	
	S.D.	37.8	31.8	36.8	36.9	
	N	25	25	24	25	

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

Table 4.2

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ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

SUMMARY OF BODY WEIGHTS (Grams)

STUDY: 218F PRECOHABITATION PHASE SEX: FEMALE

PERIOD	DOSE: GROUP:	0 1-F	3 2-F	7.5 3-F	18 4-F	(mg base/kg/day)
DAY -3	MEAN	223	223	223	222	
	S.D.	11.4	11.3	11.6	10.8	
	N	25	25	25	25	
DAY 1	MEAN	227	226	227	225	
	S.D.	12.7	12.0	11.7	12.2	
	N	25	25	25	25	
DAY 5	MEAN	231	231	230	226	
	S.D.	16.5	12.8	13.5	13.4	
	N	25	25	25	25	
DAY 8	MEAN	233	232	232	227	
	S.D.	16.7	12.7	15.2	13.9	
	N	25	25	25	25	
DAY 12	MEAN	241	240	239	232	
	S.D.	17.2	14.8	16.6	15.4	
	N	25	25	25	25	
DAY 15	MEAN	247	243	239	237	
	S.D.	16.0	17.4	18.6	16.3	
	N	25	25	24	25	

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

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ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

SUMMARY OF BODY WEIGHTS (Grams)

STUDY: 218 GESTATION PHASE SEX: FEMALE

PERIOD	DOSE: GROUP:	0 1-F	3 2-F	7.5 3-F	18 4-F	(mg base/kg/day)
GD 0	MEAN	249	250	242	236	
	S.D.	17.6	16.9	18.4	17.3	
	N	20	24	22	22	
GD 1	MEAN	258	259	252	245*	
	S.D.	17.7	17.1	17.1	18.6	
	N	20	24	22	22	
GD 2	MEAN	264	264	257	250*	
	S.D.	17.6	16.9	16.9	18.1	
	N	20	24	22	22	
GD 3	MEAN	269	268	260	252*	
	S.D.	17.3	17.8	17.4	18.5	
	N	20	24	22	22	
GD 4	MEAN	271	272	263	256*	
	S.D.	18.7	18.9	17.2	17.4	
	N	20	24	22	22	
GD 5	MEAN	275	275	266	259*	
	S.D.	17.8	17.9	17.1	18.3	
	N	20	24	22	22	
GD 6	MEAN	279	277	269	262*	
	S.D.	19.2	17.2	18.1	19.1	
	N	20	24	22	22	
GD 10	MEAN	299	297	291	282*	
	S.D.	19.3	19.1	19.1	21.7	
	N	20	24	22	22	
GD 13	MEAN	314	315	307	302	
	S.D.	21.0	19.8	20.9	23.0	
	N	20	24	22	22	
GD 16	MEAN	340	340	330	327	
	S.D.	22.8	20.2	21.9	25.1	
	N	20	23	22	22	

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

Table 5.1

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

SUMMARY OF WEIGHT GAINS (Grams)

STUDY: 218M SEX: MALE

PERIOD[a]	DOSE: / GROUP:	0 1-M	3 2-M	7.5 3-M	18 4-M	(mg base/kg/day)
DAY 5[b]	MEAN	20	15*	13*	6*	
	S.D.	4.8	4.4	4.8	5.9	
	N	25	25	25	25	
DAY 8	MEAN	13	12	13	10	
	S.D.	3.7	4.2	3.3	5.3	
	N	25	25	25	25	
DAY 12	MEAN	14	16	16	11	
	S.D.	5.5	4.4	3.8	6.4	
	N	25	25	25	25	
DAY 15	MEAN	11	9	11	2*	
	S.D.	4.2	7.1	4.8	9.2	
	N	25	25	25	25	
DAY 19	MEAN	16	12	15	10	
	S.D.	5.5	14.3	6.3	6.1	
	N	25	25	25	25	
DAY 22	MEAN	11	13	10	5*	
	S.D.	3.7	12.8	5.1	5.7	
	N	25	25	25	25	
DAY 26	MEAN	15	17	16	16	
	S.D.	3.6	4.9	6.1	7.4	
	N	25	25	25	25	
DAY 29	MEAN	2	3	1	2	
	S.D.	5.3	3.8	6.3	4.0	
	N	25	25	25	25	
DAY 33	MEAN	10	10	8	11	
	S.D.	7.2	5.3	9.7	5.0	
	N	25	25	24	25	
DAY 36	MEAN	9	9	10	8	
	S.D.	5.0	4.4	5.6	5.6	
	N	25	25	24	25	

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

[a]Weight gains compared to the previous period
[b]Baseline is day 1

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ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

SUMMARY OF WEIGHT GAINS (Grams)

STUDY: 218M SEX: MALE

PERIOD [a]	DOSE: GROUP:	0 1-M	3 2-M	7.5 3-M	18 (mg base/kg/day) 4-M
DAY 40	MEAN	15	17	16	16
	S.D.	5.5	5.3	6.1	5.8
	N	25	25	24	25
DAY 43	MEAN	9	7	7	5*
	S.D.	3.1	4.8	5.1	5.2
	N	25	25	24	25
DAY 47	MEAN	14	13	15	13
	S.D.	4.4	4.3	5.7	5.3
	N	25	25	24	25
DAY 50	MEAN	7	7	5	6
	S.D.	4.8	4.4	4.8	4.7
	N	25	25	24	25
DAY 54	MEAN	8	9	10	8
	S.D.	10.0	4.0	7.0	6.0
	N	25	25	24	25
TOTAL GAIN	MEAN	175	169	167	131*
	S.D.	28.3	21.7	30.5	28.2
	N	25	25	24	25

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

[a]Weight gains compared to the previous period

Table 5.2

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ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

SUMMARY OF WEIGHT GAINS (Grams)

STUDY: 218F PRECOHABITATION PHASE SEX: FEMALE

PERIOD[a]	DOSE: / GROUP:	0 / 1-F	3 / 2-F	7.5 / 3-F	18 / 4-F	(mg base/kg/day)
DAY 5[b]	MEAN	4	5	3	1	
	S.D.	8.2	6.9	5.1	4.4	
	N	25	25	25	25	
DAY 8	MEAN	3	2	2	1	
	S.D.	4.9	6.8	5.8	4.7	
	N	25	25	25	25	
DAY 12	MEAN	8	8	6	5	
	S.D.	4.2	5.9	3.6	5.0	
	N	25	25	25	25	
DAY 15	MEAN	6	3	2*	5	
	S.D.	4.1	5.7	5.5	4.3	
	N	25	25	24	25	
TOTAL GAIN	MEAN	20	17	13*	11*	
	S.D.	6.1	10.3	9.2	8.4	
	N	25	25	24	25	

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

[a]Weight gains compared to the previous period
[b]Baseline is day 1

Table 5.3

DRAFT

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

SUMMARY OF WEIGHT GAINS (Grams)

STUDY: 218 GESTATION PHASE SEX: FEMALE

PERIOD [a]	DOSE: GROUP:	0 1-F	3 2-F	7.5 3-F	18 4-F	(mg base/kg/day)
GD 1 [b]	MEAN	9	9	10	9	
	S.D.	4.7	3.8	4.6	5.2	
	N	20	24	22	22	
GD 2	MEAN	6	5	5	5	
	S.D.	3.3	3.6	3.6	4.2	
	N	20	24	22	22	
GD 3	MEAN	5	4	3	1*	
	S.D.	2.7	3.4	2.6	2.9	
	N	20	24	22	22	
GD 4	MEAN	2	4	3	4	
	S.D.	5.1	3.7	3.0	2.6	
	N	20	24	22	22	
GD 5	MEAN	3	3	3	3	
	S.D.	6.3	3.0	2.9	2.9	
	N	20	24	22	22	
GD 6	MEAN	4	3	3	3	
	S.D.	4.1	3.1	3.7	3.6	
	N	20	24	22	22	
GD 10	MEAN	20	20	22	21	
	S.D.	5.2	3.7	3.6	5.6	
	N	20	24	22	22	
GD 13	MEAN	16	18	17	20*	
	S.D.	3.5	5.3	5.4	4.7	
	N	20	24	22	22	
GD 16	MEAN	25	25	23	26	
	S.D.	5.5	5.6	6.2	6.0	
	N	20	23	22	22	
TOTAL GAIN	MEAN	91	90	88	91	
	S.D.	12.3	10.4	11.1	11.8	
	N	20	23	22	22	

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

[a]Weight gains compared to the previous period
[b]Baseline is gestation day 0

Table 6.1

DRAFT

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 218M SEX: MALE

PERIOD[a]	DOSE: GROUP:	0 1-M	3 2-M	7.5 3-M	18 4-M	(mg base/kg/day)
DAY -3[b]	INTAKE (g)	26.5	26.3	26.1	26.3	
	S.D.	1.84	1.85	1.65	2.03	
	N	25	25	25	25	
DAY 1	INTAKE (g)	25.4	26.0	26.1	25.5	
	S.D.	2.03	2.69	2.03	2.14	
	N	25	25	25	25	
DAY 5	INTAKE (g)	25.4	24.0*	23.0*	21.2*	
	S.D.	2.08	1.63	1.54	2.07	
	N	25	25	25	25	
DAY 8	INTAKE (g)	24.0	22.9	22.4*	20.5*	
	S.D.	2.09	1.84	1.52	2.23	
	N	25	25	25	25	
DAY 12	INTAKE (g)	25.6	25.1	25.5	22.0*	
	S.D.	2.43	1.99	1.45	2.46	
	N	25	25	25	25	
DAY 15	INTAKE (g)	24.5	24.2	24.4	20.2*	
	S.D.	2.20	1.80	1.71	2.75	
	N	25	25	25	25	
DAY 19	INTAKE (g)	25.7	24.2	25.3	20.8*	
	S.D.	2.65	4.10	1.90	3.02	
	N	25	25	25	25	
DAY 22	INTAKE (g)	25.2	24.9	25.5	21.4*	
	S.D.	2.33	2.30	2.15	2.10	
	N	25	25	25	25	

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

[a]Calculated daily food consumption for successive period intervals
[b]Baseline is day -7

Table 6.1 (contd.)

DRAFT

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 218M SEX: MALE

PERIOD[a]	DOSE: GROUP:	0 1-M	3 2-M	7.5 3-M	18 4-M	(mg base/kg/day)
DAY 26	INTAKE (g)	27.1	26.7	26.7	23.5*	
	S.D.	2.35	2.12	2.32	1.86	
	N	25	25	25	25	
DAY 29	INTAKE (g)	24.7	26.1	25.5	23.1	
	S.D.	2.18	6.00	2.65	1.74	
	N	25	25	25	25	
DAY 36	INTAKE (g)	25.5	25.1	25.2	23.3*	
	S.D.	2.14	2.91	2.20	2.12	
	N	22	23	23	24	
DAY 40	INTAKE (g)	26.6	26.4	27.6	24.4*	
	S.D.	2.28	2.46	2.35	3.15	
	N	21	24	23	24	
DAY 43	INTAKE (g)	26.6	26.2	26.4	23.7*	
	S.D.	3.01	2.64	2.66	2.65	
	N	22	24	23	24	
DAY 47	INTAKE (g)	28.2	27.6	28.4	25.8*	
	S.D.	2.42	2.24	2.66	2.51	
	N	22	24	23	24	
DAY 50	INTAKE (g)	26.3	26.0	26.5	23.4*	
	S.D.	3.39	2.65	2.16	4.43	
	N	22	24	23	24	
DAY 54	INTAKE (g)	27.6	27.8	28.3	25.9*	
	S.D.	3.07	2.09	2.40	2.20	
	N	25	25	24	25	

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

[a]Calculated daily food consumption for successive period intervals

Table 6.2

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

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SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 218F PRECOHABITATION PHASE SEX: FEMALE

PERIOD[a]	DOSE: GROUP:	0 1-F	3 2-F	7.5 3-F	18 4-F	(mg base/kg/day)
DAY -3[b]	INTAKE (g)	18.1	17.4	17.6	17.3	
	S.D.	3.23	1.78	1.75	1.85	
	N	25	25	25	25	
DAY 1	INTAKE (g)	15.8	15.7	16.2	16.1	
	S.D.	1.90	1.40	1.35	1.78	
	N	25	24	25	25	
DAY 5	INTAKE (g)	16.0	15.4	15.1	13.7*	
	S.D.	3.74	1.62	1.68	2.43	
	N	25	25	25	25	
DAY 8	INTAKE (g)	16.1	16.0	14.6*	13.0*	
	S.D.	1.49	1.17	1.88	2.68	
	N	24	25	25	25	
DAY 12	INTAKE (g)	17.6	16.8	16.0*	14.1*	
	S.D.	2.59	1.72	1.72	2.45	
	N	25	25	25	25	
DAY 15	INTAKE (g)	16.6	16.1	14.5*	13.5*	
	S.D.	1.98	2.41	1.70	1.95	
	N	25	25	24	25	

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

[a]Calculated daily food consumption for successive period intervals
[b]Baseline is day -7

Table 6.3

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 218 GESTATION PHASE SEX: FEMALE

PERIOD[a]	DOSE: GROUP:	0 1-F	3 2-F	7.5 3-F	18 4-F	(mg base/kg/day)
GD 3[b]	INTAKE (g)	20.8	19.6	18.9*	17.0*	
	S.D.	1.92	1.55	1.42	2.52	
	N	20	24	22	22	
GD 6	INTAKE (g)	21.5	22.0	18.7	17.5*	
	S.D.	1.67	6.96	2.13	2.41	
	N	20	24	22	22	
GD 10	INTAKE (g)	22.4	22.9	21.6	20.4*	
	S.D.	2.30	2.13	2.08	3.11	
	N	20	23	22	22	
GD 13	INTAKE (g)	23.5	23.8	23.3	23.7	
	S.D.	1.99	4.78	2.29	4.30	
	N	20	24	22	22	
GD 16	INTAKE (g)	24.3	24.5	23.1	24.7	
	S.D.	2.93	2.81	2.92	3.84	
	N	20	23	22	22	

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

[a]Calculated daily food consumption for successive period intervals
[b]Baseline is gestation day 0

Table 7

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT
STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

Summary of Maternal Cesarean Section Data
(Mean ± S.D.)

Dose level (mg base/kg/day)	0.0	3.0	7.5	18.0
Total Number of Females/Group	25	25	25	25
Total Number of Surviving Females	25	25	24[a]	25
Total Number of Pregnant Females	22	24	24	23
Corpora Lutea[b]	16.0 ± 2.3	16.4 ± 2.6	16.0 ± 2.8	14.7 ± 1.8
Implantation Sites[b]	15.4 ± 1.8	15.4 ± 1.5	14.3 ± 2.5	13.9 ± 1.5*
Early Resorptions[b]	0.7 ± 1.0	0.8 ± 0.8	1.2 ± 1.8	0.6 ± 0.7
Late Resorptions[b]	0	0	0	0
Viable Fetuses[b]	14.7 ± 1.8	14.5 ± 1.5	13.0 ± 3.0	13.2 ± 1.5*
Nonviable Fetuses[b]	0	0 ± 0.2	0	0
Preimplantation Loss %[b,c]	3.2 ± 5.6	5.1 ± 7.7	9.4 ± 15.6	5.3 ± 5.5
Postimplantation Loss %[b,d]	4.4 ± 5.7	5.6 ± 5.3	8.5 ± 13.8	4.2 ± 5.2
Total Implantation Loss %[b,e]	7.1 ± 8.5	10.4 ± 9.1	17.4 ± 17.8	9.0 ± 7.7

[a]One female found dead on precohabitation day 13
[b]Parameters statistically analyzed using the Kruskal-Wallis/Mann-Whitney U test ($p \leq 0.05$)
[c]Preimplantation Loss % = [(# Corpora Lutea - # Implants)/ # Corpora Lutea] x 100
[d]Postimplantation Loss % = [(# Implants - # Viable Fetuses)/ # Implants] x 100
[e]Total Implantation Loss % = [(# Corpora Lutea - # Viable Fetuses)/ # Corpora Lutea] x 100
*Statistically different from the control group

Table 8

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT
TOXICITY STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

Summary of Female Reproductive Data

Dose level (mg base/kg/day)	0	3.0	7.5	18.0
Estrus Cycle Data[a] No. (%) Cycling Normally[b]	88% (22/25)	92% (23/25)	100%[h] (24/24)	92% 23/25
Average No. Occurrences of Estrus[c]	3.68 ± 0.55	3.52 ± 0.50	3.58 ± 0.57	3.61 ± 0.49
Average Length of Estrus Cycle[c]	4.17 ± 0.49	4.27 ± 0.42	4.22 ± 0.59	4.09 ± 0.57
Mating Index[b,d]	88% (22/25)	96% (24/25)	96%[h] (23/24)	96% (24/25)
Fertility Index[b,f]	88%[g] (22/25)	96% (24/25)	96%[g,h] (23/24)	92%[g] (23/25)

[a]For the 15 day precohabitation period
[b]Statistically analyzed using the Chi-Square test
[c]Mean ± S.D.; statistically analyzed using the ANOVA/Dunnett's test ($p \leq 0.05$)
[d]Mating Index = (No. with evidence of mating/No. cohoused) x 100
[f]Fertility Index = (No. pregnant/No. with evidence of mating) x 100
[g]Two females at 0 mg base/kg/day, one female at 7.5 mg base/kg/day, and two females at 18 mg base/kg/day had evidence of mating (i.e., sperm in the vaginal washing), but were not pregnant when necropsied on gestation day 16.
[h]N = 24 pairs cohabitated (one female was found dead on precohabitation day 13)

Table 9

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT
TOXICITY STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

Summary of Male Reproductive Data

Dose Level (mg base/kg/day)	- 0	3.0	7.5	18.0
Sperm Motility[a,b] (% Motile)	97.6 ± 3.8 (25)	97.8 ± 4.5 (25)	98.1 ± 2.2 (24)[e]	99.0 ± 0.9 (25)
Sperm Count[a,b] (Million Sperm/ g Cauda Epididymis)	873.2 ± 255.8 (25)	852.3 ± 290.0[d] (24)	825.6 ± 293.3 (24)[e]	841.4 ± 271.3 (25)
Sperm Morphology[a,b] (% Abnormal)	0.3 ± 0.5 (25)	0.2 ± 0.3 (25)	0.2 ± 0.4 (24)[e]	0.3 ± 0.4 (25)
Epididymis[a,c] (% Brain Weight)	0.74 ± 0.06 (25)	0.73 ± 0.09 (25)	0.69 ± 0.05* (24)[e]	0.68 ± 0.05* (25)
Seminal Vesicles[a,c] (% Brain Weight)	0.64 ± 0.15 (25)	0.71 ± 0.19 (25)	0.64 ± 0.13 (24)[e]	0.66 ± 0.15 (25)
Prostate[a,c] (% Brain Weight)	0.34 ± 0.09 (25)	0.34 ± 0.09 (25)	0.33 ± 0.07 (24)[e]	0.31 ± 0.05 (25)
Testes[a,c] (% Brain Weight)	1.69 ± 0.13 (25)	1.65 ± 0.16 (25)	1.62 ± 0.10 (24)[e]	1.66 ± 0.16 (25)

[a]Mean ± SD; (N) = Number evaluated
[b]Statistically analyzed using the Kruskal-Wallis/Mann Whitney U test ($p \leq 0.05$)
[c]Statistically analyzed using the ANOVA/Dunnett's test ($p \leq 0.05$)
[d]Does not include one animal for which the epididymis was apparently desiccated during storage in the -70 ° freezer
[e]One male was sacrificed on study day 32 because the female with which he would have been paired was found dead prior to the initiation of the cohabitation phase, and this male was not needed for any other mating pair
*Statistically significant from control group

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APPENDIX A

ANALYTICAL CHEMISTRY REPORT

DRAFT

Oral Fertility and Early Embryonic Development Study of WR6026 Dihydrochloride in Rats

UIC/TRL STUDY NUMBER 218

Part I: **Purity Study of WR6026 Dihydrochloride**

Part II: **Analysis of WR6026 Dihydrochloride in Aqueous Solution**

Analyst: Roohi Gajee, Ph. D.

Study Site: Drug Disposition Research Laboratory
College of Pharmacy
University of Illinois at Chicago
Chicago, Illinois 60612

Sponsor: Toxicology Research Laboratory
University of Illinois at Chicago
Chicago, Illinois 60612

Report Prepared by: Roohi Gajee, Ph. D.

Report Prepared: November 6, 1996

Approved: November 6, 1996
Eugene Woods, Ph. D.
Laboratory Director

Part I: Purity Study of WR6026

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WR6026 Dihydrochloride, supplied by the Toxicology Research Laboratory (TRL) was received as a fine yellow powder and stored at -20 °C until analysis. Separate samples were received for initial and terminal purity studies.

HPLC System

Solvent Delivery System:	Waters 600E Multisolvent Delivery System
Injector:	Rheodyne: 7125 with 50 µL sample loop
Analytical Column:	Phenomenex, 10 µ, C_{18}, 300 x 3.90 mm i.d, Analytical Column S/No. 146046
Detector:	Waters 484 Tunable Absorbance Detector, 0.05 AUFS, set at 210 nm
Integrator:	Waters 746 Data Module or Spectra-Physics SP4270 integrator
Mobile Phase:	6.8 g sodium acetate and 9 mL of 85% o-phosphoric acid per liter of methanol : water, 60 : 40

Procedure

Five solutions of WR6026 in mobile phase were prepared as follows: 50 mg of a WR6026 dihydrochloride sample was weighed into a 50 mL polypropylene volumetric flask. The sample was dissolved in and the volume was brought to the mark with mobile phase. A 50 µL sample was injected into the HPLC System and chromatographed at 264 nm. This procedure was applied to determine purity on two different samples: one before the start of dosing and another after the completion of this study.

Calculation of Results

Quantitations were based on the assumption of equal detector response per unit weight of all UV-absorbing components. Area of WR6026 and other detectable components in the subject sample chromatograms were employed in the following equation to calculate the percentage of WR6026 present in the sample:

$$\% \text{ Purity} = \{\text{area of WR6026}/(\text{total area} - \text{mobile phase area})\} \times 100$$

Results

Typical chromatograms are shown in Figures 1 and 2. The samples submitted for purity analysis were found to contain <1% of UV-absorbing impurities at 264 nm. Initial purity of WR6026 was found to be 99.43 ± 0.30%. The terminal purity was established for this study and was 99.67 ± 0.04%. These results are presented in Tables 1 and 2.

Table 1: Initial purity data obtained as areas for WR6026 solutions

Peak I. D.	~Ret. Time (mins)	1	2	3	4	5
A	0.1*	-	977	-	-	-
B	0.20*	620	427	-	-	351
C	0.24	-	2638	-	-	-
D	1.52*	12256	15096	14540	14078	14542
E	1.72*	118475	132275	134032	136991	130470
F	2.0*	1304531	718280	746702	725749	700692
G	2.26	-	188552	190961	189231	185561
H	2.69*	34113	93567	98485	100676	88847
I	3.12*	32967	73206	79727	73418	65425
J	4.13	28461264	27565310	28475911	28491590	29782567
K	5.70	12042	11081	10797	11128	11192
[a] %Purity per run		99.96	99.27	99.30	99.30	99.34

[a] % Purity per run = {area of WR6026/(total area - mobile phase area)} x 100
* Area due to Mobile Phase

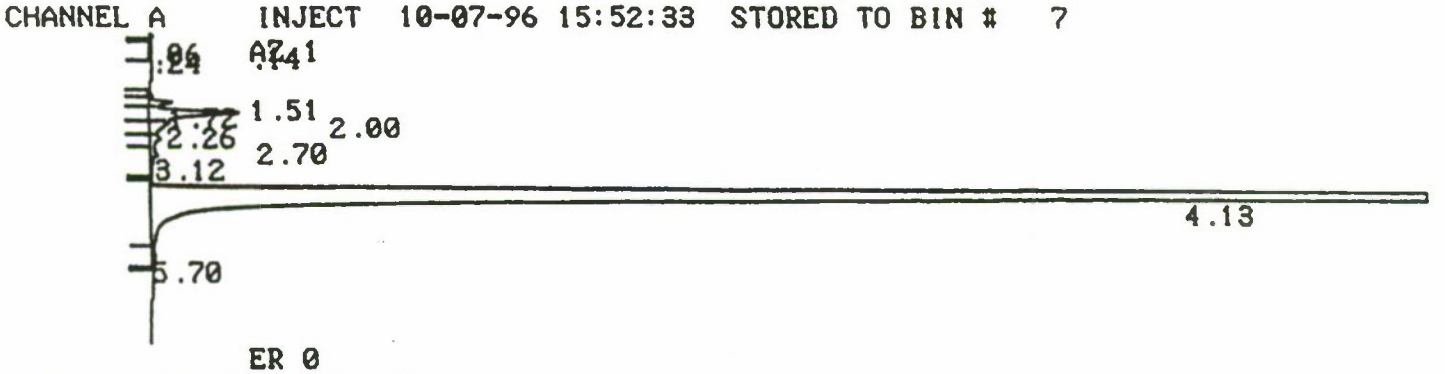
Table 2: Terminal purity data obtained as areas for WR6026 solutions

Peak I. D.	~Ret. Time (mins)	1	2	3	4	5
A	0.11*	4103	-	-	-	-
B	0.20*	-	367	395	200	-
C	0.44	32061	-	-	-	-
D	0.7	-	13210	13048	13178	12433
E	0.84	4467	-	-	-	-
F	1.1	-	765	276	-	-
G	1.34*	48898	9725	9794	12326	12639
H	1.55*	-	2943	3021	-	-
I	1.91	17425	12330	11739	10334	12328
J	2.11	40322	37996	37353	42716	38816
K	2.34	8014	5725	5930	-	8455
L	2.54	9901	8591	9081	9195	12457
M	2.81	10518	12176	12137	12364	13228
N	3.11	2301	3188	3405	3104	3231
O	3.83	31729001	30907325	30571086	30074842	30616231
P	5.18	2926	4232	4383	-	2814
[a] %Purity per run		99.60	99.69	99.68	99.70	99.66

[a] % Purity per run = {area of WR6026/(total area - mobile phase area)} x 100

* Area due to Mobile Phase

Figure 1: Initial purity chromatogram for WR6026

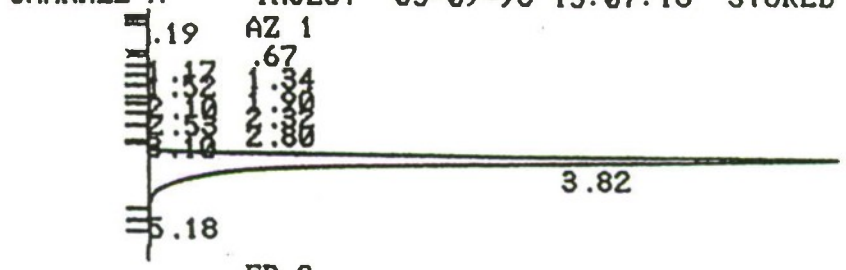


WR6026 INITIAL PURITY 10-07-96 15:52:33 CH= "A" PS= 1.

FILE 1. METHOD 0. RUN 9 INDEX 9 BIN 7

PEAK#	AREA%	RT	AREA BC	PEAK I. D
1	0.003	0.06	977 02	A
2	0.001	0.14	427 02	B
3	0.009	0.24	2638 03	C
4	0.052	1.51	15096 02	D
5	0.459	1.72	132275 02	E
6	2.494	2.	718280 02	F
7	0.655	2.26	188552 02	G
8	0.325	2.7	93567 02	H
9	0.254	3.12	73226 03	I
10	95.708	4.13	27565310 08	J
11	0.038	5.7	11081 05	K
TOTAL	100.		28801429	

Figure 2: Terminal purity chromatogram for WR6026



WR 6026 TERMINAL PURITY 05-09-96 15:07:18 CH= "A" PS= 1.

FILE 1. METHOD 0. RUN 16 INDEX 16 BIN 15

PEAK#	AREA%	RT	AREA BC	PEAK I.D
1	0.001	0.19	395 01	B
2	0.043	0.67	13048 02	D
3	0.001	1.17	276 02	F
4	0.032	1.34	9794 02	G
5	0.01	1.52	3021 02	H
6	0.038	1.9	11739 02	I
7	0.122	2.1	37353 02	J
8	0.019	2.32	5930 02	K
9	0.03	2.53	9081 02	L
10	0.04	2.8	12137 02	M
11	0.011	3.1	3405 03	N
12	99.64	3.82	30571086 08	O
13	0.014	5.18	4383 05	P
TOTAL	100.		30681648	

Part II: Analysis of WR6026 Dosing Suspensions

Samples for UIC/TRL Study No. 218 were submitted by the TRL to the Drug Disposition Research Laboratory for quantitation of WR6026 in aqueous solution. Samples were received on July 11, 1996, July 18, 1996, July 25, 1996, August 1, 1996, August 8, 1996, August 15, 1996, August 22, 1996 and August 29, 1996. All samples submitted were analyzed by HPLC as described earlier in this report. Standard solutions and controls were prepared and analyzed as described below. Adjustment was made for purity and for the mole fraction of standards, controls and samples.

Methodology:

See HPLC System: page 2 of this report.

Standards and Controls

Class A volumetric pipettes were used for all diluting procedures.

Preparation of standards[b]: theoretical amount

a. 1.0 mg/mL calibration stock solution of WR6026 in mobile phase.
100 mg of WR6026 was weighed and transferred to a 100 mL volumetric flask. Sufficient mobile phase was added to dissolve the solid. The volume was adjusted to the mark with the mobile phase.

b. 100 µg/mL calibration standard solution of WR6026 in mobile phase.
10 mL of the WR6026 calibration stock solution was transferred to a 100 mL volumetric flask and diluted to the mark with additional mobile phase.

c. 80 µg/mL calibration standard solution of WR6026 in mobile phase.
8 mL of the 100 µg/mL calibration standard solution was transferred to a 10 mL volumetric flask and diluted to the mark with additional mobile phase.

d. 60 µg/mL calibration standard solution of WR606 in mobile phase.
6 mL of the 100 µg/mL calibration standard solution was transferred to a 10 mL volumetric flask and diluted to the mark with additional mobile phase.

e. 40 µg/mL calibration standard solution of WR6026 in mobile phase.
4 mL of the 100 µg/mL calibration standard solution was transferred to a 10 mL volumetric flask and diluted to the mark with additional mobile phase.

f. 20 µg/mL calibration standard solution of WR6026 in mobile phase.
2 mL of the 100 µg/mL calibration standard solution was transferred to a 10 mL volumetric flask and diluted to the mark with additional mobile phase.

g. 10 µg/mL calibration standard solution of WR6026 in mobile phase.

1 mL of the 100 µg/mL calibration standard solution was transferred to a 10 mL volumetric flask and diluted to the mark with additional mobile phase.

Preparation of controls[b]: The controls were prepared independent of the analyst to validate the standard curve.

a. High control: 3 mg/mL

A 75 mg sample of WR6026 was transferred to a 25 mL volumetric flask. Sufficient mobile phase was added to dissolve the contents and the volume was adjusted to the mark with additional mobile phase. A 1 mL aliquot of this 3 mg/mL solution was transferred to a 25 mL volumetric flask, mixed and the volume was adjusted to the mark with sufficient amount of mobile phase. Using a glass pipet, 10 mL of this solution was transferred to another 25 mL volumetric flask, mixed and the volume was adjusted to the mark with mobile phase. The final concentration of this WR6026 solution is 48 µg/mL (dilution 1 : 62.5).

b. Low control: 1 mg/mL

A 25 mg of WR6026 was transferred to a 25 mL volumetric flask. Sufficient mobile phase was added to dissolve the contents and the volume was adjusted to the mark with additional mobile phase. A 1 mL aliquotof 1 mg/mL solution was transferred to a 25 mL volumetric flask, mixed and the volume was adjusted to the mark with additional mobile phase. The final concentration of this WR6026 solution is 40 µg/mL (dilution 1 : 25).

Analytical method

Samples for UIC/TRL Study No. 218 were received by the Drug Disposition Research Laboratory for quantitation of WR6026 in aqueous solution. All samples submitted were analyzed by HPLC as described earlier in this report. Standard solutions and controls were prepared and analyzed as described above. Adjustment was made for purity of samples. A sample standard curve is shown in Figure 3.

Results

Results of analysis of dosing formulation for UIC/TRL Study No. 218 are found in Tables 3, 4, 5, 6, 7, 8, 9 and 10. All dosing formulations analyzed were within 10% of their target values. It should be noted that for week 5 the 3.6 mg/mL solution on initial analysis was outside the 10% allowable error range. It was adjusted, submitted and reanalyzed the following day.

[b] in the first set of analysis, the concentration of the standard curve and control solutions were doubled the concentration stated.

Figure 3: A representative standard curve solution graph for WR6026

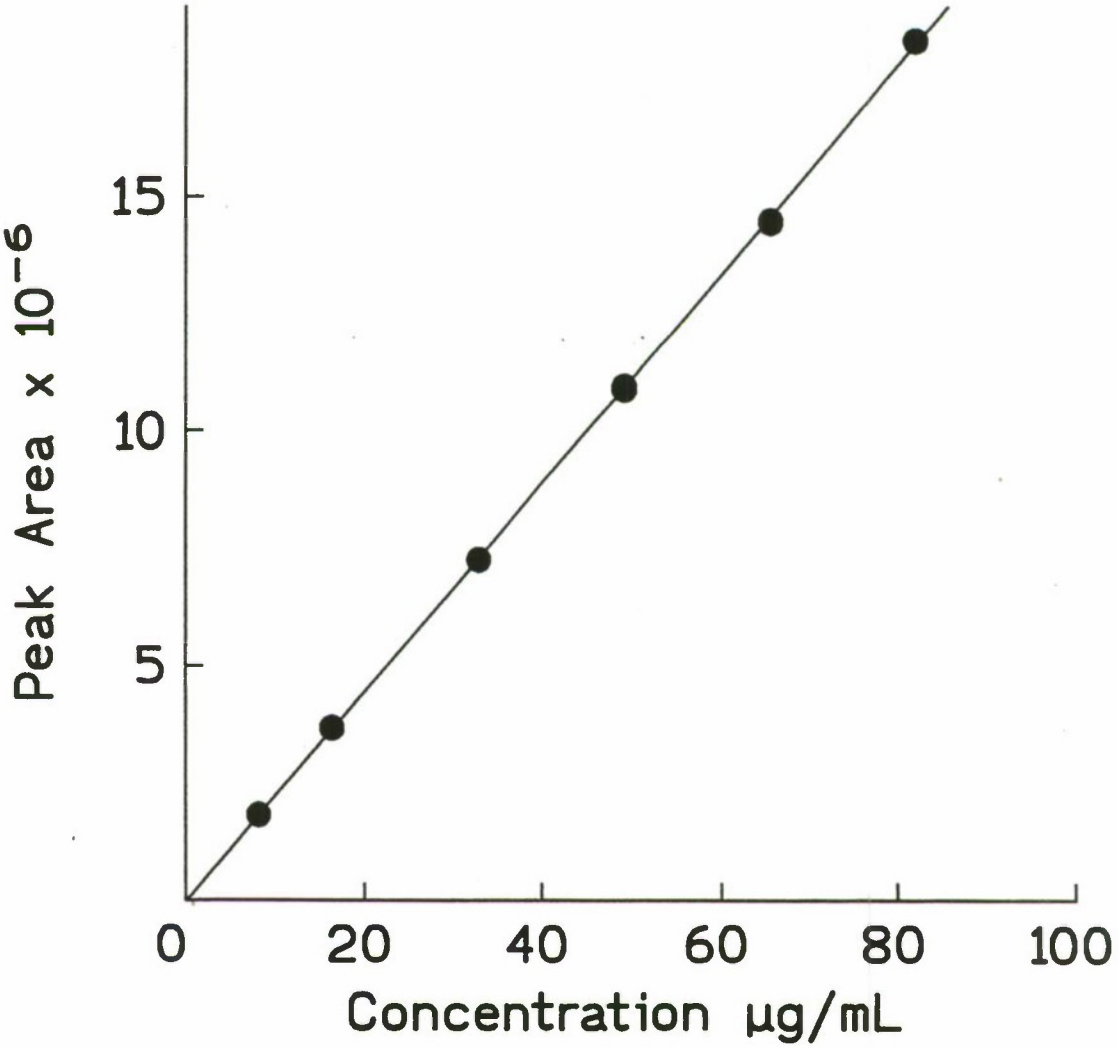


Table 3: Results of dosing solutions for Study No. 218, week 1.

Sample Identification	Target concentration (mg/mL)	Mean Concentration ± S. D.
White	0	0
Teal	0.6	0.579 ± 0.008
Rose	1.5	1.382 ± 0.013
Gold	3.6	3.526 ± 0.051

Table 4: Results of dosing solutions for Study No. 218, week 2.

Sample Identification	Target concentration (mg/mL)	Mean Concentration ± S. D.
White	0	0
Teal	0.6	0.618 ± 0.021
Rose	1.5	1.500 ± 0.033
Gold	3.6	3.448 ± 0.037

Table 5: Results of dosing solutions for Study No. 218, week 3.

Sample Identification	Target concentration (mg/mL)	Mean Concentration ± S. D.
White	0	0
Teal	0.6	0.587 ± 0.010
Rose	1.5	1.500 ± 0.035
Gold	3.6	3.417 ± 0.058

Table 6: Results of dosing solutions for Study No. 218, week 4.

Sample Identification	Target concentration (mg/mL)	Mean Concentration ± S. D.
White	0	0
Teal	0.6	0.604 ± 0.001
Rose	1.5	1.523 ± 0.001
Gold	3.6	3.692 ± 0.011

Table 7: Results of dosing solutions for Study No. 218, week 5.

Sample Identification	Target concentration (mg/mL)	Mean Concentration ± S. D.
White	0	0
Teal	0.6	0.604 ± 0.016
Rose	1.5	1.540 ± 0.006
Gold	3.6	3.626 ± 0.092

Table 8: Results of dosing solutions for Study No. 218, week 6.

Sample Identification	Target concentration (mg/mL)	Mean Concentration ± S. D.
White	0	0
Teal	0.6	0.610 ± 0.008
Rose	1.5	1.387 ± 0.025
Gold	3.6	3.639 ± 0.051

Table 9: Results of dosing solutions for Study No. 218, week 7.

Sample Identification	Target concentration (mg/mL)	Mean Concentration ± S. D.
White	0	0
Teal	0.6	0.610 ± 0.001
Rose	1.5	1.529 ± 0.001
Gold	3.6	3.557 ± 0.053

Table 10: Results of dosing solutions for Study No. 218, week 8.

Sample Identification	Target concentration (mg/mL)	Mean Concentration ± S. D.
White	0	0
Teal	0.6	0.600 ± 0.008
Rose	1.5	1.428 ± 0.025
Gold	3.6	3.495 ± 0.055

APPENDIX B

INDIVIDUAL MALE DATA

- Individual Observations
- Individual Body Weights
- Individual Weight Gain
- Individual Daily Food Consumption

ORAL FERTILITY AND EARLY EMBRYONIC
DEVELOPMENT STUDY OF
WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL CLINICAL SIGNS

STUDY: 218M GROUP: 1-M SEX: MALE
DAY 1-DAY 57 DOSE: 0(mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
501	Normal			DAY 1-DAY 55
	Scheduled Sacrifice			DAY 56
502	Normal			DAY 1-DAY 56
	Scheduled Sacrifice			DAY 57
503	Normal			DAY 1-DAY 54
	Scheduled Sacrifice			DAY 55
504	Normal			DAY 1-DAY 54
	Scheduled Sacrifice			DAY 55
505	Normal			DAY 1-DAY 54
	Scheduled Sacrifice			DAY 55
506	Normal			DAY 1-DAY 54
	Scheduled Sacrifice			DAY 55
507	Normal			DAY 1-DAY 55
	Scheduled Sacrifice			DAY 56
508	Normal			DAY 1-DAY 55
	Scheduled Sacrifice			DAY 56
509	Normal			DAY 1-DAY 56
	Scheduled Sacrifice			DAY 57
510	Normal			DAY 1-DAY 55
	Scheduled Sacrifice			DAY 56
511	Normal			DAY 1-DAY 54
	Scheduled Sacrifice			DAY 55
512	Normal			DAY 1-DAY 56
	Scheduled Sacrifice			DAY 57
513	Normal			DAY 1-DAY 55
	Scheduled Sacrifice			DAY 56

ORAL FERTILITY AND EARLY EMBRYONIC
DEVELOPMENT STUDY OF
WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL CLINICAL SIGNS

STUDY: 218M GROUP: 1-M SEX: MALE
DAY 1-DAY 57 DOSE: 0 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
514	Normal			DAY 1-DAY 54
	Scheduled Sacrifice			DAY 55
515	Normal			DAY 1-DAY 56
	Scheduled Sacrifice			DAY 57
516	Normal			DAY 1-DAY 54
	Scheduled Sacrifice			DAY 55
517	Normal			DAY 1-DAY 55
	Scheduled Sacrifice			DAY 56
518	Normal			DAY 1-DAY 56
	Scheduled Sacrifice			DAY 57
519	Normal			DAY 1-DAY 56
	Scheduled Sacrifice			DAY 57
520	Normal			DAY 1-DAY 55
	Scheduled Sacrifice			DAY 56
521	Normal			DAY 1-DAY 54
	Scheduled Sacrifice			DAY 55
522	Normal			DAY 1-DAY 55
	Scheduled Sacrifice			DAY 56
523	Normal			DAY 1-DAY 55
	Scheduled Sacrifice			DAY 56
524	Normal			DAY 1-DAY 55
	Scheduled Sacrifice			DAY 56
525	Normal			DAY 1-DAY 54
	Scheduled Sacrifice			DAY 55

ORAL FERTILITY AND EARLY EMBRYONIC
DEVELOPMENT STUDY OF
WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL CLINICAL SIGNS

STUDY: 218M GROUP: 2-M SEX: MALE
DAY 1-DAY 57 DOSE: 3 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
526	Normal			DAY 1-DAY 54
	Scheduled Sacrifice			DAY 55
527	Normal			DAY 1-DAY 54
	Scheduled Sacrifice			DAY 55
528	Normal			DAY 1-DAY 56
	Scheduled Sacrifice			DAY 57
529	Normal			DAY 1-DAY 55
	Scheduled Sacrifice			DAY 56
530	Normal			DAY 1-DAY 55
	Scheduled Sacrifice			DAY 56
531	Normal			DAY 1-DAY 56
	Scheduled Sacrifice			DAY 57
532	Normal			DAY 1-DAY 55
	Scheduled Sacrifice			DAY 56
533	Normal			DAY 1-DAY 54
	Scheduled Sacrifice			DAY 55
534	Normal			DAY 1-DAY 55
	Scheduled Sacrifice			DAY 56
535	Normal			DAY 1-DAY 54
	Scheduled Sacrifice			DAY 55
536	Normal			DAY 1-DAY 54
	Scheduled Sacrifice			DAY 55
537	Normal			DAY 1-DAY 55
	Scheduled Sacrifice			DAY 56
538	Normal			DAY 1-DAY 55
	Scheduled Sacrifice			DAY 56

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF
WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL CLINICAL SIGNS

STUDY: 218M GROUP: 2-M SEX: MALE
DAY 1-DAY 57 DOSE: 3 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
539	Normal			DAY 1-DAY 55
	Scheduled Sacrifice			DAY 56
540	Normal			DAY 1-DAY 55
	Scheduled Sacrifice			DAY 56
541	Normal			DAY 1-DAY 55
	Scheduled Sacrifice			DAY 56
542	Normal			DAY 1-DAY 56
	Scheduled Sacrifice			DAY 57
543	Normal			DAY 1-DAY 54
	Scheduled Sacrifice			DAY 55
544	Normal			DAY 1-DAY 54
	Scheduled Sacrifice			DAY 55
545	Normal			DAY 1-DAY 54
	Scheduled Sacrifice			DAY 55
546	Normal			DAY 1-DAY 54
	Scheduled Sacrifice			DAY 55
547	Normal			DAY 1-DAY 54
	Scheduled Sacrifice			DAY 55
548	Normal			DAY 1-DAY 55
	Scheduled Sacrifice			DAY 56
549	Normal			DAY 1-DAY 55
	Scheduled Sacrifice			DAY 56
550	Normal			DAY 1-DAY 54
	Scheduled Sacrifice			DAY 55

ORAL FERTILITY AND EARLY EMBRYONIC
DEVELOPMENT STUDY OF
WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL CLINICAL SIGNS

STUDY: 218M GROUP: 3-M SEX: MALE
DAY 1-DAY 57 DOSE: 7.5 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
551	Normal			DAY 1-DAY 54
	Scheduled Sacrifice			DAY 55
552	Normal			DAY 1-DAY 54
	Scheduled Sacrifice			DAY 55
553	Normal			DAY 1-DAY 55
	Scheduled Sacrifice			DAY 56
554	Normal			DAY 1-DAY 56
	Scheduled Sacrifice			DAY 57
555	Normal			DAY 1-DAY 55
	Scheduled Sacrifice			DAY 56
556	Normal			DAY 1-DAY 56
	Scheduled Sacrifice			DAY 57
557	Normal			DAY 1-DAY 55
	Scheduled Sacrifice			DAY 56
558	Normal			DAY 1-DAY 55
	Scheduled Sacrifice			DAY 56
559	Normal			DAY 1-DAY 54
	Scheduled Sacrifice			DAY 55
560[a]	Normal			DAY 1-DAY 32
	Sacrificed			DAY 32
561	Normal			DAY 1-DAY 56
	Scheduled Sacrifice			DAY 57
562	Normal			DAY 1-DAY 54
	Scheduled Sacrifice			DAY 55
563	Normal			DAY 1-DAY 55
	Scheduled Sacrifice			DAY 56

[a]Animal No. 560 at 7.5 mg base/kg/day was removed from the study on day 32. The female with which it would have been paired was found dead on precohabitation day 13, and this male was not needed for any other mating pair in the mid dose group.

ORAL FERTILITY AND EARLY EMBRYONIC
DEVELOPMENT STUDY OF
WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL CLINICAL SIGNS

STUDY: 218M GROUP: 3-M SEX: MALE
DAY 1-DAY 57 DOSE: 7.5(mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
564	Normal			DAY 1-DAY 55
	Scheduled Sacrifice			DAY 56
565	Normal			DAY 1-DAY 56
	Scheduled Sacrifice			DAY 57
566	Normal			DAY 1-DAY 56
	Scheduled Sacrifice			DAY 57
567	Normal			DAY 1-DAY 54
	Scheduled Sacrifice			DAY 55
568	Normal			DAY 1-DAY 55
	Scheduled Sacrifice			DAY 56
569	Normal			DAY 1-DAY 55
	Scheduled Sacrifice			DAY 56
570	Normal			DAY 1-DAY 56
	Scheduled Sacrifice			DAY 57
571	Normal			DAY 1-DAY 55
	Scheduled Sacrifice			DAY 56
572	Normal			DAY 1-DAY 55
	Scheduled Sacrifice			DAY 56
573	Normal			DAY 1-DAY 55
	Scheduled Sacrifice			DAY 56
574	Normal			DAY 1-DAY 55
	Scheduled Sacrifice			DAY 56
575	Normal			DAY 1-DAY 56
	Scheduled Sacrifice			DAY 57

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

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INDIVIDUAL CLINICAL SIGNS

STUDY: 218M GROUP: 4-M SEX: MALE
DAY 1-DAY 57 DOSE: 18(mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
576	Blue Tongue			DAY 13-DAY 14
	Blue Tongue			DAY 21-DAY 22
	Normal			DAY 1-DAY 12
	Normal			DAY 15-DAY 20
	Normal			DAY 23-DAY 54
	Scheduled Sacrifice			DAY 55
577	Blue Tongue			DAY 13-DAY 17
	Blue Tongue			DAY 19
	Blue Tongue			DAY 21-DAY 23
	Blue Tongue			DAY 26
	Blue Tongue			DAY 28
	Blue Tongue			DAY 33
	Blue Tongue			DAY 37
	Blue Tongue			DAY 42
	Blue Tongue			DAY 48
	Blue Tongue			DAY 52
	Normal			DAY 1-DAY 12
	Normal			DAY 18
	Normal			DAY 20
	Normal			DAY 24-DAY 25
	Normal			DAY 27
	Normal			DAY 29-DAY 32
	Normal			DAY 34-DAY 36
	Normal			DAY 38-DAY 41
	Normal			DAY 43-DAY 47
	Normal			DAY 49-DAY 51
	Normal			DAY 53-DAY 55
	Scheduled Sacrifice			DAY 56
578	Blue Tongue			DAY 45
	Normal			DAY 1-DAY 44
	Normal			DAY 46-DAY 54
	Scheduled Sacrifice			DAY 55
579	Blue Tongue			DAY 52
	Normal			DAY 1-DAY 51
	Normal			DAY 53-DAY 55
	Scheduled Sacrifice			DAY 56

ORAL FERTILITY AND EARLY EMBRYONIC
DEVELOPMENT STUDY OF
WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL CLINICAL SIGNS

STUDY: 218M GROUP: 4-M SEX: MALE
DAY 1-DAY 57 DOSE: 18(mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
580	Normal			DAY 1-DAY 55
	Scheduled Sacrifice			DAY 56
581	Blue Tongue			DAY 14
	Blue Tongue			DAY 16-DAY 17
	Blue Tongue			DAY 23
	Blue Tongue			DAY 33
	Normal			DAY 1-DAY 13
	Normal			DAY 15
	Normal			DAY 18-DAY 22
	Normal			DAY 24-DAY 32
	Normal			DAY 34-DAY 55
	Scheduled Sacrifice			DAY 56
582	Normal			DAY 1-DAY 54
	Scheduled Sacrifice			DAY 55
583	Normal			DAY 1-DAY 56
	Scheduled Sacrifice			DAY 57
584	Blue Tongue			DAY 26
	Blue Tongue			DAY 31
	Normal			DAY 1-DAY 25
	Normal			DAY 27-DAY 30
	Normal			DAY 32-DAY 55
	Scheduled Sacrifice			DAY 56
585	Normal			DAY 1-DAY 55
	Scheduled Sacrifice			DAY 56
586	Normal			DAY 1-DAY 55
	Scheduled Sacrifice			DAY 56
587	Blue Tongue			DAY 31
	Normal			DAY 1-DAY 30
	Normal			DAY 32-DAY 55
	Scheduled Sacrifice			DAY 56

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL CLINICAL SIGNS

STUDY: 218M GROUP: 4-M SEX: MALE
DAY 1-DAY 57 DOSE: 18 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
588	Normal			DAY 1-DAY 54
	Scheduled Sacrifice			DAY 55
589	Blue Tongue			DAY 16-DAY 17
	Blue Tongue			DAY 35
	Normal			DAY 1-DAY 15
	Normal			DAY 18-DAY 34
	Normal			DAY 36-DAY 54
	Scheduled Sacrifice			DAY 55
590	Normal			DAY 1-DAY 54
	Scheduled Sacrifice			DAY 55
591	Blue Tongue			DAY 13
	Blue Tongue			DAY 27
	Normal			DAY 1-DAY 12
	Normal			DAY 14-DAY 26
	Normal			DAY 28-DAY 55
	Scheduled Sacrifice			DAY 56
592	Blue Tongue			DAY 17
	Blue Tongue			DAY 44
	Normal			DAY 1-DAY 16
	Normal			DAY 18-DAY 43
	Normal			DAY 45-DAY 55
	Scheduled Sacrifice			DAY 56
593	Blue Tongue			DAY 22-DAY 23
	Normal			DAY 1-DAY 21
	Normal			DAY 24-DAY 56
	Scheduled Sacrifice			DAY 57
594	Blue Tongue			DAY 36
	Normal			DAY 1-DAY 35
	Normal			DAY 37-DAY 54
	Scheduled Sacrifice			DAY 55
595	Normal			DAY 1-DAY 55
	Scheduled Sacrifice			DAY 56

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ORAL FERTILITY AND EARLY EMBRYONIC
DEVELOPMENT STUDY OF
WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL CLINICAL SIGNS

STUDY: 218M GROUP: 4-M SEX: MALE
DAY 1-DAY 57 DOSE: 18(mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
596	Normal			DAY 1-DAY 54
	Scheduled Sacrifice			DAY 55
597	Normal			DAY 1-DAY 54
	Scheduled Sacrifice			DAY 55
598	Normal			DAY 1-DAY 56
	Scheduled Sacrifice			DAY 57
599	Normal			DAY 1-DAY 56
	Scheduled Sacrifice			DAY 57
600	Normal			DAY 1-DAY 55
	Scheduled Sacrifice			DAY 56

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ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INCIDENCE OF OBSERVATIONS

STUDY: 218M SEX: MALE

PERIOD	DOSE:(mg base/kg/day) GROUP:	0 1-M	3 2-M	7.5 3-M	18 4-M
DAY 1					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%
DAY 2					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%
DAY 3					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%
DAY 4					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%
DAY 5					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%
DAY 6					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%
DAY 7					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%
DAY 8					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%
DAY 9					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%
DAY 10					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%

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ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INCIDENCE OF OBSERVATIONS

STUDY: 218M SEX: MALE

PERIOD	DOSE:(mg base/kg/day) GROUP:	0 1-M	3 2-M	7.5 3-M	18 4-M
DAY 11					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%
DAY 12					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%
DAY 13					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	22 88%
Blue Tongue		0	0	0	3 12%
DAY 14					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	22 88%
Blue Tongue		0	0	0	3 12%
DAY 15					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	24 96%
Blue Tongue		0	0	0	1 4%
DAY 16					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	22 88%
Blue Tongue		0	0	0	3 12%
DAY 17					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	21 84%
Blue Tongue		0	0	0	4 16%
DAY 18					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%
DAY 19					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	24 96%
Blue Tongue		0	0	0	1 4%

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INCIDENCE OF OBSERVATIONS

STUDY: 218M SEX: MALE

PERIOD	DOSE: (mg base/kg/day) / GROUP:	0 / 1-M	3 / 2-M	7.5 / 3-M	18 / 4-M
DAY 20					
	No. Observed	25	25	25	25
	Normal	25 100%	25 100%	25 100%	25 100%
DAY 21					
	No. Observed	25	25	25	25
	Normal	25 100%	25 100%	25 100%	23 92%
	Blue Tongue	0	0	0	2 8%
DAY 22					
	No. Observed	25	25	25	25
	Normal	25 100%	25 100%	25 100%	22 88%
	Blue Tongue	0	0	0	3 12%
DAY 23					
	No. Observed	25	25	25	25
	Normal	25 100%	25 100%	25 100%	22 88%
	Blue Tongue	0	0	0	3 12%
DAY 24					
	No. Observed	25	25	25	25
	Normal	25 100%	25 100%	25 100%	25 100%
DAY 25					
	No. Observed	25	25	25	25
	Normal	25 100%	25 100%	25 100%	25 100%
DAY 26					
	No. Observed	25	25	25	25
	Normal	25 100%	25 100%	25 100%	23 92%
	Blue Tongue	0	0	0	2 8%
DAY 27					
	No. Observed	25	25	25	25
	Normal	25 100%	25 100%	25 100%	24 96%
	Blue Tongue	0	0	0	1 4%
DAY 28					
	No. Observed	25	25	25	25
	Normal	25 100%	25 100%	25 100%	24 96%
	Blue Tongue	0	0	0	1 4%

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ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INCIDENCE OF OBSERVATIONS

STUDY: 218M SEX: MALE

PERIOD	DOSE:(mg base/kg/day) GROUP:	0 1-M	3 2-M	7.5 3-M	18 4-M
DAY 29					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%
DAY 30					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%
DAY 31					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	23 92%
Blue Tongue		0	0	0	2 8%
DAY 32					
No. Observed		25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%
Sacrificed[a]		0	0	1 4%	0
DAY 33					
No. Observed		25	25	24	25
Normal		25 100%	25 100%	24 100%	23 92%
Blue Tongue		0	0	0	2 8%
DAY 34					
No. Observed		25	25	24	25
Normal		25 100%	25 100%	24 100%	25 100%
DAY 35					
No. Observed		25	25	24	25
Normal		25 100%	25 100%	24 100%	24 96%
Blue Tongue		0	0	0	1 4%
DAY 36					
No. Observed		25	25	24	25
Normal		25 100%	25 100%	24 100%	24 96%
Blue Tongue		0	0	0	1 4%
DAY 37					
No. Observed		25	25	24	25
Normal		25 100%	25 100%	24 100%	24 96%
Blue Tongue		0	0	0	1 4%

[a]One male at 7.5 mg base/kg/day was sacrificed on day 32 because the female with which he would have been paired was found dead on precohabitation day 13, and this male was not needed for any other mating pair in the mid dose group.

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INCIDENCE OF OBSERVATIONS

STUDY: 218M SEX: MALE

PERIOD	DOSE:(mg base/kg/day) GROUP:	0 1-M	3 2-M	7.5 3-M	18 4-M
DAY 38					
No. Observed		25	25	24	25
Normal		25 100%	25 100%	24 100%	25 100%
DAY 39					
No. Observed		25	25	24	25
Normal		25 100%	25 100%	24 100%	25 100%
DAY 40					
No. Observed		25	25	24	25
Normal		25 100%	25 100%	24 100%	25 100%
DAY 41					
No. Observed		25	25	24	25
Normal		25 100%	25 100%	24 100%	25 100%
DAY 42					
No. Observed		25	25	24	25
Normal		25 100%	25 100%	24 100%	24 96%
Blue Tongue		0	0	0	1 4%
DAY 43					
No. Observed		25	25	24	25
Normal		25 100%	25 100%	24 100%	25 100%
DAY 44					
No. Observed		25	25	24	25
Normal		25 100%	25 100%	24 100%	24 96%
Blue Tongue		0	0	0	1 4%
DAY 45					
No. Observed		25	25	24	25
Normal		25 100%	25 100%	24 100%	24 96%
Blue Tongue		0	0	0	1 4%
DAY 46					
No. Observed		25	25	24	25
Normal		25 100%	25 100%	24 100%	25 100%

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ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INCIDENCE OF OBSERVATIONS

STUDY: 218M SEX: MALE

PERIOD	DOSE: (mg base/kg/day) GROUP:	0 1-M	3 2-M	7.5 3-M	18 4-M
DAY 47					
	No. Observed	25	25	24	25
	Normal	25 100%	25 100%	24 100%	25 100%
DAY 48					
	No. Observed	25	25	24	25
	Normal	25 100%	25 100%	24 100%	24 96%
	Blue Tongue	0	0	0	1 4%
DAY 49					
	No. Observed	25	25	24	25
	Normal	25 100%	25 100%	24 100%	25 100%
DAY 50					
	No. Observed	25	25	24	25
	Normal	25 100%	25 100%	24 100%	25 100%
DAY 51					
	No. Observed	25	25	24	25
	Normal	25 100%	25 100%	24 100%	25 100%
DAY 52					
	No. Observed	25	25	24	25
	Normal	25 100%	25 100%	24 100%	23 92%
	Blue Tongue	0	0	0	2 8%
DAY 53					
	No. Observed	25	25	24	25
	Normal	25 100%	25 100%	24 100%	25 100%
DAY 54					
	No. Observed	25	25	24	25
	Normal	25 100%	25 100%	24 100%	25 100%
DAY 55					
	No. Observed	25	25	24	25
	Scheduled Sacrifice	9 36%	11 44%	5 21%	9 36%
	Normal	16 64%	14 56%	19 79%	16 64%
DAY 56					
	No. Observed	16	14	19	16
	Scheduled Sacrifice	10 62%	11 79%	12 63%	12 75%
	Normal	6 38%	3 21%	7 37%	4 25%
DAY 57					
	No. Observed	6	3	7	4
	Scheduled Sacrifice	6 100%	3 100%	7 100%	4 100%

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 218M GROUP: 1-M SEX: MALE
DOSE: 0 (mg base/kg/day)

ANIMAL #	DAY -3	DAY 1	DAY 5	DAY 8	DAY 12	DAY 15	DAY 19	DAY 22	DAY 26	DAY 29	DAY 33	DAY 36
501	335	343	358	376	386	393	408	413	426	430	442	447
502	329	342	357	368	384	393	403	411	424	432	437	443
503	355	372	395	404	421	426	442	448	462	466	476	488
504	348	364	385	396	411	417	435	444	459	459	456	468
505	344	349	369	374	395	399	416	428	447	441	455	464
506	359	361	386	400	418	428	440	458	472	472	479	488
507	345	352	376	392	405	408	432	439	462	452	475	485
508	355	371	393	405	424	440	463	469	488	495	504	507
509	341	360	383	398	407	423	441	451	463	463	480	486
510	338	353	374	395	410	426	445	459	476	490	489	503
511	351	368	386	397	413	430	445	461	474	477	491	514
512	365	381	408	426	446	457	482	497	518	511	514	527
513	332	347	366	375	388	406	415	425	441	445	452	464
514	348	367	383	394	408	421	433	444	456	464	477	489
515	347	361	382	396	413	424	439	445	461	461	460	469
516	324	335	343	352	356	369	379	389	401	403	408	416
517	335	345	365	379	383	396	407	422	432	430	448	455
518	333	347	361	371	373	386	411	417	432	432	441	453
519	362	379	398	414	437	447	469	480	495	495	518	519
520	361	369	391	406	418	433	443	456	467	473	486	492
521	358	373	394	413	427	439	457	472	494	495	500	512
522	348	357	379	393	414	424	443	456	474	479	485	500
523	338	352	365	377	387	393	404	414	423	423	431	438
524	350	362	392	407	427	440	459	474	489	485	508	507
525	352	353	378	390	406	417	421	430	444	450	460	464
MEAN	346	359	379	392	406	417	433	444	459	461	471	480
S.D.	11.1	12.2	15.3	16.9	20.7	21.3	24.0	25.4	27.3	27.0	28.0	28.4
N	25	25	25	25	25	25	25	25	25	25	25	25

--: Data Unavailable

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ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 218M GROUP: 1-M SEX: MALE
DOSE: 0 (mg base/kg/day)

ANIMAL #	DAY 40	DAY 43	DAY 47	DAY 50	DAY 54
501	460	461	473	478	480
502	463	471	490	503	506
503	496	508	515	528	538
504	481	492	505	508	524
505	477	485	495	502	510
506	506	512	531	532	539
507	512	522	532	537	513
508	521	531	554	558	576
509	503	517	527	535	548
510	518	527	544	553	563
511	535	545	558	572	585
512	537	548	566	581	595
513	477	488	499	499	512
514	499	508	516	533	539
515	490	493	507	514	519
516	424	431	442	448	462
517	471	479	495	502	482
518	461	474	488	489	503
519	539	549	571	571	580
520	505	516	531	536	543
521	534	546	558	570	587
522	516	525	546	555	566
523	441	454	466	469	485
524	528	540	559	565	577
525	482	488	504	507	515
MEAN	495	504	519	526	534
S.D.	31.0	32.0	33.8	35.3	37.8
N	25	25	25	25	25

--: Data Unavailable

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ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 218M GROUP: 2-M SEX: MALE
DOSE: 3 (mg base/kg/day)

ANIMAL #	DAY -3	DAY 1	DAY 5	DAY 8	DAY 12	DAY 15	DAY 19	DAY 22	DAY 26	DAY 29	DAY 33	DAY 36
526	349	359	370	383	396	412	424	440	454	461	475	489
527	338	350	369	382	398	411	417	421	436	441	447	449
528	363	377	391	401	417	427	447	457	480	485	491	507
529	346	347	367	379	396	412	426	443	463	469	482	492
530	356	365	372	382	399	378	325	397	420	431	438	451
531	345	356	372	386	396	405	422	428	440	442	444	451
532	357	368	391	397	419	433	448	461	483	490	495	507
533	334	350	368	383	402	411	429	442	459	463	478	484
534	327	340	352	364	376	384	397	408	426	427	434	443
535	360	371	391	408	429	442	458	475	489	496	506	511
536	339	352	368	377	396	405	420	426	445	451	458	469
537	342	358	370	377	396	406	428	442	457	466	466	473
538	330	335	345	359	368	376	391	403	418	418	434	442
539	327	334	347	349	359	367	375	382	398	396	408	415
540	355	371	386	401	424	427	443	452	474	471	478	485
541	335	357	372	379	394	402	422	426	457	456	465	468
542	353	357	377	393	409	423	437	450	468	469	475	491
543	334	340	348	352	365	373	380	390	405	403	419	419
544	341	352	365	378	386	398	414	424	429	431	437	440
545	361	376	384	397	413	423	447	458	478	481	493	501
546	351	366	381	394	411	424	434	443	455	455	476	487
547	351	373	390	411	418	431	447	454	473	474	486	494
548	348	359	377	390	408	416	430	438	455	456	475	484
549	347	374	385	394	409	416	431	444	459	459	466	477
550	363	378	399	413	434	449	468	478	497	505	508	525
MEAN	346	359	373	385	401	410	422	435	453	456	465	474
S.D.	11.1	13.2	14.7	16.9	19.2	21.5	30.3	24.9	26.0	27.4	26.6	28.9
N	25	25	25	25	25	25	25	25	25	25	25	25

--: Data Unavailable

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ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 218M GROUP: 2-M SEX: MALE
DOSE: 3 (mg base/kg/day)

ANIMAL #	DAY 40	DAY 43	DAY 47	DAY 50	DAY 54
526	498	511	520	523	533
527	462	481	487	503	514
528	526	533	550	554	561
529	500	507	519	528	534
530	480	489	506	509	522
531	469	475	489	493	501
532	526	537	544	545	548
533	504	512	527	528	534
534	460	462	475	484	489
535	526	538	557	558	560
536	483	484	498	508	515
537	489	500	517	526	541
538	460	468	483	492	499
539	427	426	436	437	452
540	502	504	519	526	531
541	494	493	504	511	520
542	508	516	524	541	546
543	433	441	451	452	465
544	454	464	472	479	488
545	518	525	545	555	568
546	493	497	515	527	541
547	512	517	522	528	542
548	500	504	520	527	542
549	504	518	534	541	554
550	542	553	569	576	587
MEAN	491	498	511	518	527
S.D.	29.4	30.7	32.1	32.5	31.8
N	25	25	25	25	25

--: Data Unavailable

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ORAL FERTILITY AND EARLY EMBRYONIC
DEVELOPMENT STUDY OF
WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 218M GROUP: 3-M SEX: MALE
DOSE: 7.5 (mg base/kg/day)

ANIMAL #	DAY -3	DAY 1	DAY 5	DAY 8	DAY 12	DAY 15	DAY 19	DAY 22	DAY 26	DAY 29	DAY 33	DAY 36
551	333	351	370	377	392	402	413	420	434	433	439	449
552	330	344	355	365	377	386	397	407	418	416	430	436
553	361	374	380	395	410	427	441	455	476	486	494	513
554	346	351	372	378	392	396	410	419	430	428	442	448
555	351	361	374	382	400	409	428	434	453	459	459	472
556	347	346	361	374	387	398	409	412	423	422	428	439
557	337	356	363	375	392	408	421	421	439	437	455	460
558	343	357	374	387	396	415	420	431	445	445	457	466
559	321	340	343	355	365	370	376	399	395	371	400	413
560[a]	330	343	355	365	382	392	404	412	430	428	--	--
561	344	359	368	377	389	398	410	416	426	426	433	445
562	354	369	387	403	427	440	466	483	503	512	519	526
563	341	359	378	392	409	418	443	461	475	472	484	483
564	354	373	386	398	415	432	445	455	469	471	487	498
565	360	376	386	400	417	432	449	457	484	486	495	506
566	348	364	381	391	407	411	425	434	446	448	459	458
567	356	370	391	403	424	441	459	470	489	496	506	524
568	367	393	404	419	436	440	454	464	482	482	456	478
569	363	376	386	401	419	433	442	451	469	472	492	496
570	334	350	363	378	402	409	436	450	471	473	478	492
571	338	354	361	379	396	403	414	427	439	444	445	455
572	359	371	379	395	407	425	435	441	458	465	474	481
573	340	350	360	378	395	412	433	442	466	466	469	483
574	351	363	377	394	413	422	451	469	490	492	498	511
575	348	363	373	384	404	416	430	437	456	457	463	476
MEAN	346	361	373	386	402	413	428	439	455	455	465	475
S.D.	11.7	12.7	13.6	14.5	16.4	18.1	21.3	22.3	26.7	31.2	28.8	29.6
N	25	25	25	25	25	25	25	25	25	25	24	24

--: Data Unavailable

[a]Animal No. 560 at 7.5 mg base/kg/day was removed from the study on day 32. The female with which it would have been paired was found dead on precohabitation day 13, and this male was not needed for any other mating pair in the mid dose group.

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

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INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 218M GROUP: 3-M SEX: MALE
DOSE: 7.5(mg base/kg/day)

ANIMAL #	DAY 40	DAY 43	DAY 47	DAY 50	DAY 54
551	463	468	483	485	497
552	447	457	473	480	489
553	525	538	546	559	571
554	465	469	477	478	489
555	485	489	505	511	533
556	453	459	474	478	489
557	467	475	477	482	492
558	477	486	500	505	515
559	431	436	445	456	464
560[a]	--	--	--	--	--
561	461	465	473	475	485
562	553	561	589	588	606
563	514	515	526	525	530
564	511	517	538	545	543
565	530	538	556	563	579
566	470	478	490	496	506
567	543	553	570	581	584
568	493	517	532	530	541
569	507	519	536	546	537
570	516	519	539	540	549
571	463	469	482	488	501
572	497	501	510	512	526
573	500	507	527	530	540
574	537	533	555	548	574
575	492	498	515	526	537
MEAN	492	499	513	518	528
S.D.	32.7	33.1	36.6	36.3	36.8
N	24	24	24	24	24

--: Data Unavailable

[a]Animal No. 560 at 7.5 mg base/kg/day was removed from the study on day 32. The female with which it would have been paired was found dead on precohabitation day 13, and this male was not needed for any other mating pair in the mid dose group.

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

DRAFT

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 218M GROUP: 4-M SEX: MALE
DOSE: 18 (mg base/kg/day)

ANIMAL #	DAY -3	DAY 1	DAY 5	DAY 8	DAY 12	DAY 15	DAY 19	DAY 22	DAY 26	DAY 29	DAY 33	DAY 36
576	337	350	358	362	365	355	366	381	386	386	398	410
577	352	362	374	375	384	389	395	403	412	419	421	436
578	360	375	389	405	426	437	454	459	473	472	482	492
579	334	348	354	366	368	372	375	383	393	398	403	411
580	339	353	361	379	389	395	404	412	423	423	430	438
581	333	340	342	346	356	359	375	381	389	387	398	405
582	349	359	372	376	392	398	412	414	431	431	443	446
583	346	361	363	379	386	395	403	409	418	421	432	446
584	356	371	365	374	378	378	386	394	406	404	423	416
585	347	357	365	380	399	407	413	420	440	441	451	458
586	351	367	368	383	391	403	404	413	429	428	436	450
587	350	360	368	379	389	392	404	404	423	420	426	422
588	336	349	354	364	380	395	405	414	431	429	447	451
589	331	347	356	371	383	360	390	398	426	434	445	450
590	348	363	369	374	388	382	395	385	402	403	420	422
591	323	335	332	342	341	333	346	355	366	370	379	385
592	345	353	357	359	371	377	383	391	400	404	407	420
593	368	388	399	405	426	436	443	454	476	481	496	505
594	362	378	396	412	431	437	449	453	460	470	478	492
595	327	327	339	345	352	332	347	340	373	371	385	398
596	343	360	361	370	381	381	394	403	434	428	450	463
597	358	369	376	382	388	393	398	404	423	425	440	449
598	361	378	390	402	424	431	447	454	476	482	488	501
599	355	374	379	393	407	411	412	411	428	436	443	453
600	340	354	349	368	372	373	383	380	391	392	405	410
MEAN	346	359	365	376	387	389	399	405	420	422	433	441
S.D.	11.7	14.3	16.9	18.2	23.1	28.9	28.1	29.1	29.9	31.0	31.0	32.3
N	25	25	25	25	25	25	25	25	25	25	25	25

--: Data Unavailable

ORAL FERTILITY AND EARLY EMBRYONIC
DEVELOPMENT STUDY OF
WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 218M GROUP: 4-M SEX: MALE
DOSE: 18 (mg base/kg/day)

ANIMAL #	DAY 40	DAY 43	DAY 47	DAY 50	DAY 54
576	419	426	431	437	456
577	451	456	476	486	496
578	503	515	526	533	539
579	418	419	436	436	442
580	452	447	468	468	474
581	423	421	440	450	450
582	464	463	467	476	486
583	470	472	484	488	500
584	435	440	450	448	461
585	475	479	498	498	511
586	457	468	488	488	505
587	446	452	465	466	479
588	473	478	488	492	504
589	465	472	482	494	504
590	442	450	465	472	483
591	393	395	401	410	414
592	441	451	458	466	470
593	522	539	555	561	563
594	503	504	517	522	525
595	424	436	452	461	470
596	476	482	497	495	515
597	463	468	483	492	490
598	525	530	548	559	566
599	475	481	500	506	505
600	419	414	418	434	436
MEAN	457	462	476	482	490
S.D.	33.3	35.4	37.3	37.0	36.9
N	25	25	25	25	25

--: Data Unavailable

ORAL FERTILITY AND EARLY EMBRYONIC
DEVELOPMENT STUDY OF
WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 218M GROUP: 1-M SEX: MALE
DOSE: 0 (mg base/kg/day)

ANIMAL #	DAY 5[b]	DAY 8	DAY 12	DAY 15	DAY 19	DAY 22	DAY 26	DAY 29	DAY 33	DAY 36	DAY 40
501	15	18	10	7	15	5	13	4	12	5	13
502	15	11	16	9	10	8	13	8	5	6	20
503	23	9	17	5	16	6	14	4	10	12	8
504	21	11	15	6	18	9	15	0	-3	12	13
505	20	5	21	4	17	12	19	-6	14	9	13
506	25	14	18	10	12	18	14	0	7	9	18
507	24	16	13	3	24	7	23	-10	23	10	27
508	22	12	19	16	23	6	19	7	9	3	14
509	23	15	9	16	18	10	12	0	17	6	17
510	21	21	15	16	19	14	17	14	-1	14	15
511	18	11	16	17	15	16	13	3	14	23	21
512	27	18	20	11	25	15	21	-7	3	13	10
513	19	9	13	18	9	10	16	4	7	12	13
514	16	11	14	13	12	11	12	8	13	12	10
515	21	14	17	11	15	6	16	0	-1	9	21
516	8	9	4	13	10	10	12	2	5	8	8
517	20	14	4	13	11	15	10	-2	18	7	16
518	14	10	2	13	25	6	15	0	9	12	8
519	19	16	23	10	22	11	15	0	23	1	20
520	22	15	12	15	10	13	11	6	13	6	13
521	21	19	14	12	18	15	22	1	5	12	22
522	22	14	21	10	19	13	18	5	6	15	16
523	13	12	10	6	11	10	9	0	8	7	3
524	30	15	20	13	19	15	15	-4	23	-1	21
525	25	12	16	11	4	9	14	6	10	4	18
MEAN	20	13	14	11	16	11	15	2	10	9	15
S.D.	4.8	3.7	5.5	4.2	5.5	3.7	3.6	5.3	7.2	5.0	5.5
N	25	25	25	25	25	25	25	25	25	25	25

--: Data Unavailable

[a]Weight gains compared to the previous period
[b]Baseline is day 1

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INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 218M GROUP: 1-M SEX: MALE
DOSE: 0 (mg base/kg/day)

ANIMAL #	DAY 43	DAY 47	DAY 50	DAY 54	TOTAL GAIN
501	1	12	5	2	137
502	8	19	13	3	164
503	12	7	13	10	166
504	11	13	3	16	160
505	8	10	7	8	161
506	6	19	1	7	178
507	10	10	5	-24	161
508	10	23	4	18	205
509	14	10	8	13	188
510	9	17	9	10	210
511	10	13	14	13	217
512	11	18	15	14	214
513	11	11	0	13	165
514	9	8	17	6	172
515	3	14	7	5	158
516	7	11	6	14	127
517	8	16	7	-20	137
518	13	14	1	14	156
519	10	22	0	9	201
520	11	15	5	7	174
521	12	12	12	17	214
522	9	21	9	11	209
523	13	12	3	16	133
524	12	19	6	12	215
525	6	16	3	8	162
MEAN	9	14	7	8	175
S.D.	3.1	4.4	4.8	10.0	28.3
N	25	25	25	25	25

--: Data Unavailable

[a]Weight gains compared to the previous period

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ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 218M GROUP: 2-M SEX: MALE
DOSE: 3 (mg base/kg/day)

ANIMAL #	DAY 5[b]	DAY 8	DAY 12	DAY 15	DAY 19	DAY 22	DAY 26	DAY 29	DAY 33	DAY 36	DAY 40
526	11	13	13	16	12	16	14	7	14	14	9
527	19	13	16	13	6	4	15	5	6	2	13
528	14	10	16	10	20	10	23	5	6	16	19
529	20	12	17	16	14	17	20	6	13	10	8
530	7	10	17	-21	-53	72	23	11	7	13	29
531	16	14	10	9	17	6	12	2	2	7	18
532	23	6	22	14	15	13	22	7	5	12	19
533	18	15	19	9	18	13	17	4	15	6	20
534	12	12	12	8	13	11	18	1	7	9	17
535	20	17	21	13	16	17	14	7	10	5	15
536	16	9	19	9	15	6	19	6	7	11	14
537	12	7	19	10	22	14	15	9	0	7	16
538	10	14	9	8	15	12	15	0	16	8	18
539	13	2	10	8	8	7	16	-2	12	7	12
540	15	15	23	3	16	9	22	-3	7	7	17
541	15	7	15	8	20	4	31	-1	9	3	26
542	20	16	16	14	14	13	18	1	6	16	17
543	8	4	13	8	7	10	15	-2	16	0	14
544	13	13	8	12	16	10	5	2	6	3	14
545	8	13	16	10	24	11	20	3	12	8	17
546	15	13	17	13	10	9	12	0	21	11	6
547	17	21	7	13	16	7	19	1	12	8	18
548	18	13	18	8	14	8	17	1	19	9	16
549	11	9	15	7	15	13	15	0	7	11	27
550	21	14	21	15	19	10	19	8	3	17	17
MEAN	15	12	16	9	12	13	17	3	10	9	17
S.D.	4.4	4.2	4.4	7.1	14.3	12.8	4.9	3.8	5.3	4.4	5.3
N	25	25	25	25	25	25	25	25	25	25	25

--: Data Unavailable

[a]Weight gains compared to the previous period
[b]Baseline is day 1

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

DRAFT

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 218M GROUP: 2-M SEX: MALE
DOSE: 3 (mg base/kg/day)

ANIMAL #	DAY 43	DAY 47	DAY 50	DAY 54	TOTAL GAIN
526	13	9	3	10	174
527	19	6	16	11	164
528	7	17	4	7	184
529	7	12	9	6	187
530	9	17	3	13	157
531	6	14	4	8	145
532	11	7	1	3	180
533	8	15	1	6	184
534	2	13	9	5	149
535	12	19	1	2	189
536	1	14	10	7	163
537	11	17	9	15	183
538	8	15	9	7	164
539	-1	10	1	15	118
540	2	15	7	5	160
541	-1	11	7	9	163
542	8	8	17	5	189
543	8	10	1	13	125
544	10	8	7	9	136
545	7	20	10	13	192
546	4	18	12	14	175
547	5	5	6	14	169
548	4	16	7	15	183
549	14	16	7	13	180
550	11	16	7	11	209
MEAN	7	13	7	9	169
S.D.	4.8	4.3	4.4	4.0	21.7
N	25	25	25	25	25

--: Data Unavailable

[a]Weight gains compared to the previous period

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 218M GROUP: 3-M SEX: MALE
DOSE: 7.5 (mg base/kg/day)

ANIMAL #	DAY 5[b]	DAY 8	DAY 12	DAY 15	DAY 19	DAY 22	DAY 26	DAY 29	DAY 33	DAY 36	DAY 40
551	19	7	15	10	11	7	14	-1	6	10	14
552	11	10	12	9	11	10	11	-2	14	6	11
553	6	15	15	17	14	14	21	10	8	19	12
554	21	6	14	4	14	9	11	-2	14	6	17
555	13	8	18	9	19	6	19	6	0	13	13
556	15	13	13	11	11	3	11	-1	6	11	14
557	7	12	17	16	13	0	18	-2	18	5	7
558	17	13	9	19	5	11	14	0	12	9	11
559	3	12	10	5	6	23	-4	-24	29	13	18
560[c]	12	10	17	10	12	8	18	-2	--	--	--
561	9	9	12	9	12	6	10	0	7	12	16
562	18	16	24	13	26	17	20	9	7	7	27
563	19	14	17	9	25	18	14	-3	12	-1	31
564	13	12	17	17	13	10	14	2	16	11	13
565	10	14	17	15	17	8	27	2	9	11	24
566	17	10	16	4	14	9	12	2	11	-1	12
567	21	12	21	17	18	11	19	7	10	18	19
568	11	15	17	4	14	10	18	0	-26	22	15
569	10	15	18	14	9	9	18	3	20	4	11
570	13	15	24	7	27	14	21	2	5	14	24
571	7	18	17	7	11	13	12	5	1	10	8
572	8	16	12	18	10	6	17	7	9	7	16
573	10	18	17	17	21	9	24	0	3	14	17
574	14	17	19	9	29	18	21	2	6	13	26
575	10	11	20	12	14	7	19	1	6	13	16
MEAN	13	13	16	11	15	10	16	1	8	10	16
S.D.	4.8	3.3	3.8	4.8	6.3	5.1	6.1	6.3	9.7	5.6	6.1
N	25	25	25	25	25	25	25	25	24	24	24

--: Data Unavailable

[a]Weight gains compared to the previous period
[b]Baseline is day 1
[c]Animal No. 560 at 7.5 mg base/kg/day was removed from the study on day 32. The female with which it would have been paired was found dead on precohabitation day 13, and this male was not needed for any other mating pair in the mid dose group.

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

DRAFT

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 218M GROUP: 3-M SEX: MALE
DOSE: 7.5 (mg base/kg/day)

ANIMAL #	DAY 43	DAY 47	DAY 50	DAY 54	TOTAL GAIN
551	5	15	2	12	146
552	10	16	7	9	145
553	13	8	13	12	197
554	4	8	1	11	138
555	4	16	6	22	172
556	6	15	4	11	143
557	8	2	5	10	136
558	9	14	5	10	158
559	5	9	11	8	124
560[b]	--	--	--	--	--
561	4	8	2	10	126
562	8	28	-1	18	237
563	1	11	-1	5	171
564	6	21	7	-2	170
565	8	18	7	16	203
566	8	12	6	10	142
567	10	17	11	3	214
568	24	15	-2	11	148
569	12	17	10	-9	161
570	3	20	1	9	199
571	6	13	6	13	147
572	4	9	2	14	155
573	7	20	3	10	190
574	-4	22	-7	26	211
575	6	17	11	11	174
MEAN	7	15	5	10	167
S.D.	5.1	5.7	4.8	7.0	30.5
N	24	24	24	24	24

--: Data Unavailable

[a]Weight gains compared to the previous period

[b]Animal No. 560 at 7.5 mg base/kg/day was removed from the study on day 32. The female with which it would have been paired was found dead on precohabitation day 13, and this male was not needed for any other mating pair in the mid dose group.

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 218M GROUP: 4-M SEX: MALE
DOSE: 18 (mg base/kg/day)

ANIMAL #	DAY 5[b]	DAY 8	DAY 12	DAY 15	DAY 19	DAY 22	DAY 26	DAY 29	DAY 33	DAY 36	DAY 40
576	8	4	3	-10	11	15	5	0	12	12	9
577	12	1	9	5	6	8	9	7	2	15	15
578	14	16	21	11	17	5	14	-1	10	10	11
579	6	12	2	4	3	8	10	5	5	8	7
580	8	18	10	6	9	8	11	0	7	8	14
581	2	4	10	3	16	6	8	-2	11	7	18
582	13	4	16	6	14	2	17	0	12	3	18
583	2	16	7	9	8	6	9	3	11	14	24
584	-6	9	4	0	8	8	12	-2	19	-7	19
585	8	15	19	8	6	7	20	1	10	7	17
586	1	15	8	12	1	9	16	-1	8	14	7
587	8	11	10	3	12	0	19	-3	6	-4	24
588	5	10	16	15	10	9	17	-2	18	4	22
589	9	15	12	-23	30	8	28	8	11	5	15
590	6	5	14	-6	13	-10	17	1	17	2	20
591	-3	10	-1	-8	13	9	11	4	9	6	8
592	4	2	12	6	6	8	9	4	3	13	21
593	11	6	21	10	7	11	22	5	15	9	17
594	18	16	19	6	12	4	7	10	8	14	11
595	12	6	7	-20	15	-7	33	-2	14	13	26
596	1	9	11	0	13	9	31	-6	22	13	13
597	7	6	6	5	5	6	19	2	15	9	14
598	12	12	22	7	16	7	22	6	6	13	24
599	5	14	14	4	1	-1	17	8	7	10	22
600	-5	19	4	1	10	-3	11	1	13	5	9
MEAN	6	10	11	2	10	5	16	2	11	8	16
S.D.	5.9	5.3	6.4	9.2	6.1	5.7	7.4	4.0	5.0	5.6	5.8
N	25	25	25	25	25	25	25	25	25	25	25

--: Data Unavailable

[a]Weight gains compared to the previous period
[b]Baseline is day 1

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 218M GROUP: 4-M SEX: MALE
DOSE: 18 (mg base/kg/day)

ANIMAL #	DAY 43	DAY 47	DAY 50	DAY 54	TOTAL GAIN
576	7	5	6	19	106
577	5	20	10	10	134
578	12	11	7	6	164
579	1	17	0	6	94
580	-5	21	0	6	121
581	-2	19	10	0	110
582	-1	4	9	10	127
583	2	12	4	12	139
584	5	10	-2	13	90
585	4	19	0	13	154
586	11	20	0	17	138
587	6	13	1	13	119
588	5	10	4	12	155
589	7	10	12	10	157
590	8	15	7	11	120
591	2	6	9	4	79
592	10	7	8	4	117
593	17	16	6	2	175
594	1	13	5	3	147
595	12	16	9	9	143
596	6	15	-2	20	155
597	5	15	9	-2	121
598	5	18	11	7	188
599	6	19	6	-1	131
600	-5	4	16	2	82
MEAN	5	13	6	8	131
S.D.	5.2	5.3	4.7	6.0	28.2
N	25	25	25	25	25

--: Data Unavailable

[a]Weight gains compared to the previous period

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 218M GROUP: 1-M SEX: MALE
DOSE: 0 (mg base/kg/day)

ANIMAL #	DAY -3[b]	DAY 1	DAY 5	DAY 8	DAY 12	DAY 15	DAY 19	DAY 22	DAY 26	DAY 29	DAY 36	DAY 40
501	23.8	23.7	22.5	23.0	23.0	23.3	24.0	23.3	24.5	23.3	23.0	24.8
502	23.3	23.3	23.8	21.7	22.8	23.0	22.8	22.7	25.0	23.0	23.0	25.8
503	26.5	27.3	26.8	24.7	28.0	26.0	26.3	25.7	28.0	26.0	25.3	27.3
504	28.0	28.3	28.0	25.3	27.8	27.0	27.8	27.3	29.0	26.7	24.7	27.3
505	25.5	23.7	23.8	22.0	25.5	22.3	23.8	23.3	25.5	22.7	--	--
506	28.5	26.7	26.8	25.0	27.0	26.0	26.3	27.0	28.0	24.7	25.3	27.8
507	26.5	23.7	25.5	23.7	24.3	22.7	24.0	24.7	27.8	22.3	--	--
508	29.0	28.3	27.5	25.7	28.8	27.0	31.5	27.7	29.8	27.3	27.0	29.5
509	24.8	24.7	25.5	24.7	25.0	25.0	25.5	25.0	26.3	24.0	25.3	26.8
510	24.8	26.3	25.5	25.7	25.8	24.7	26.5	26.7	27.8	26.7	26.0	27.3
511	25.8	26.0	27.0	25.7	26.5	26.7	26.8	27.0	28.3	27.7	29.0	30.0
512	30.0	27.3	30.0	29.0	30.3	29.0	31.5	30.0	33.0	28.7	27.7	--
513	25.5	21.7	23.5	22.7	24.0	22.7	23.3	23.7	26.0	23.7	23.0	25.0
514	26.3	25.7	25.3	22.7	23.5	23.7	24.8	22.3	26.3	23.0	24.7	25.5
515	26.5	24.3	25.0	23.7	25.0	24.7	25.0	24.7	26.0	23.3	25.0	24.8
516	24.5	23.7	21.3	20.3	21.3	21.3	22.0	22.3	23.8	20.3	23.0	22.0
517	26.0	24.0	24.0	22.7	23.3	22.0	23.5	24.3	25.0	22.3	25.0	24.8
518	24.3	24.3	22.0	21.0	21.5	20.3	24.0	22.3	24.3	23.0	26.3	23.3
519	27.5	26.7	25.5	24.0	27.0	25.3	27.0	26.7	27.3	25.7	25.7	28.8
520	26.3	24.3	24.5	23.0	24.0	24.0	24.3	24.3	26.5	24.7	24.7	26.0
521	30.5	30.7	29.3	27.7	28.3	26.7	28.5	29.7	31.8	28.3	29.7	31.8
522	28.0	25.7	26.3	23.7	28.3	25.3	27.8	27.3	30.0	26.0	30.0	27.3
523	25.5	25.7	24.5	21.7	23.5	21.3	20.8	22.0	23.8	22.7	--	--
524	27.8	26.7	25.3	27.0	28.3	27.0	28.5	27.0	27.0	26.7	26.0	27.3
525	26.5	23.3	25.8	24.0	26.5	25.3	26.3	23.3	26.5	25.0	22.3	25.5
MEAN	26.5	25.4	25.4	24.0	25.6	24.5	25.7	25.2	27.1	24.7	25.5	26.6
S.D.	1.84	2.03	2.08	2.09	2.43	2.20	2.65	2.33	2.35	2.18	2.14	2.28
N	25	25	25	25	25	25	25	25	25	25	22	21

--: Data Unavailable

[a]Calculated daily food consumption for successive period intervals
[b]Baseline is day -7

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 218M GROUP: 1-M SEX: MALE
DOSE: 0 (mg base/kg/day)

ANIMAL #	DAY 43	DAY 47	DAY 50	DAY 54
501	22.3	24.8	23.7	24.0
502	23.7	26.5	26.0	26.0
503	26.7	27.5	28.3	28.8
504	27.3	28.0	26.3	30.0
505	--	--	--	26.3
506	26.0	28.8	27.0	29.0
507	--	--	--	24.8
508	29.3	32.0	29.7	32.3
509	27.0	27.8	26.0	27.0
510	26.7	29.0	28.7	29.0
511	29.3	30.8	32.0	32.0
512	34.7	32.3	32.7	33.8
513	25.3	26.3	21.0	23.8
514	25.0	27.3	24.7	26.3
515	27.0	27.8	20.3	26.8
516	21.3	22.8	22.0	23.5
517	24.7	27.3	25.7	24.8
518	24.0	25.8	22.3	24.8
519	27.0	29.8	27.3	27.8
520	25.7	26.5	25.3	26.8
521	31.7	31.8	31.7	33.0
522	28.3	31.0	27.0	31.0
523	--	--	--	23.5
524	28.3	29.3	27.3	28.0
525	24.0	27.3	24.0	26.3
MEAN	26.6	28.2	26.3	27.6
S.D.	3.01	2.42	3.39	3.07
N	22	22	22	25

--: Data Unavailable

[a]Calculated daily food consumption for successive period intervals

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 218M GROUP: 2-M SEX: MALE
DOSE: 3 (mg base/kg/day)

ANIMAL #	DAY -3[b]	DAY 1	DAY 5	DAY 8	DAY 12	DAY 15	DAY 19	DAY 22	DAY 26	DAY 29	DAY 36	DAY 40
526	26.0	24.3	23.3	21.7	22.8	24.3	24.8	24.7	25.8	25.3	25.0	25.5
527	26.3	23.7	23.0	23.3	26.0	24.0	24.0	22.7	25.3	23.7	24.3	25.5
528	30.0	29.0	26.5	24.0	28.3	26.7	28.3	26.7	30.3	26.7	29.0	30.5
529	27.3	21.3	24.3	22.7	24.8	24.3	25.0	26.0	27.8	24.7	--	--
530	27.8	27.0	23.0	22.7	25.0	21.3	7.0	29.7	30.5	27.7	24.3	28.5
531	27.0	26.3	25.0	24.3	24.8	23.7	24.8	23.0	24.5	53.0	21.0	24.0
532	28.3	26.7	24.8	23.0	26.8	27.3	27.3	26.3	29.0	29.3	27.0	29.8
533	25.3	27.7	25.3	24.0	27.0	26.3	27.8	27.0	28.5	27.3	27.0	29.0
534	24.0	23.0	22.8	21.3	23.0	23.0	23.8	22.3	25.5	24.0	23.7	25.3
535	25.5	26.7	23.3	24.7	27.8	24.3	25.8	28.0	29.5	27.0	27.7	25.5
536	26.0	24.7	23.3	22.3	24.5	23.7	25.0	24.3	26.8	25.3	28.3	26.3
537	25.8	23.3	21.5	21.0	24.3	22.3	24.5	24.7	25.5	23.0	--	24.8
538	25.5	22.0	21.8	21.3	22.0	22.3	22.8	22.7	24.0	22.3	23.7	24.0
539	24.3	22.3	22.8	21.0	22.0	23.0	21.3	22.3	23.5	21.3	22.7	24.5
540	26.5	25.3	25.0	23.0	26.5	24.3	23.8	27.7	28.0	25.7	27.0	27.8
541	20.5	29.0	24.5	19.3	24.3	22.0	23.0	20.3	26.0	22.3	24.3	26.8
542	28.5	26.3	27.3	26.7	28.0	27.0	27.8	27.0	28.3	27.3	27.3	29.0
543	24.8	22.3	20.5	18.7	22.0	21.3	20.5	22.3	23.3	21.7	21.0	22.8
544	25.3	25.3	22.5	22.0	22.8	21.7	22.8	22.0	23.8	22.7	18.0	20.3
545	26.3	31.3	24.0	22.7	24.5	25.7	25.8	25.3	26.8	25.3	26.3	26.0
546	27.8	29.3	25.0	25.0	27.8	26.3	26.3	24.3	27.0	25.3	26.7	26.8
547	26.3	29.0	24.3	25.0	24.5	25.0	24.3	24.3	26.3	24.0	23.3	26.0
548	27.0	27.3	26.0	23.0	24.0	24.3	24.8	26.0	27.5	24.7	27.7	26.5
549	27.0	28.7	24.0	24.7	25.5	24.7	24.5	24.7	25.5	23.7	22.3	27.8
550	28.3	27.0	26.3	24.0	27.3	26.0	28.0	27.3	29.5	28.3	29.7	30.5
MEAN	26.3	26.0	24.0	22.9	25.1	24.2	24.2	24.9	26.7	26.1	25.1	26.4
S.D.	1.85	2.69	1.63	1.84	1.99	1.80	4.10	2.30	2.12	6.00	2.91	2.46
N	25	25	25	25	25	25	25	25	25	25	23	24

--: Data Unavailable

[a]Calculated daily food consumption for successive period intervals
[b]Baseline is day -7

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 218M GROUP: 2-M SEX: MALE
DOSE: 3 (mg base/kg/day)

ANIMAL #	DAY 43	DAY 47	DAY 50	DAY 54
526	25.3	26.3	25.0	26.5
527	27.3	26.8	28.3	28.3
528	28.3	29.8	27.7	30.3
529	--	--	--	25.3
530	27.0	29.0	27.7	29.3
531	23.3	25.3	23.3	24.3
532	28.3	29.5	27.7	28.5
533	29.7	31.3	27.7	29.0
534	23.0	26.3	24.3	27.5
535	31.3	29.0	27.7	27.3
536	26.0	28.5	26.3	27.8
537	24.7	26.8	24.3	27.3
538	24.0	25.5	24.7	25.5
539	21.0	24.0	22.3	25.0
540	22.3	28.0	24.3	30.3
541	25.0	25.8	26.0	26.8
542	28.3	28.8	29.7	29.5
543	22.3	23.3	22.7	23.8
544	29.0	25.0	18.7	26.3
545	27.0	29.3	28.0	28.5
546	25.7	30.0	28.7	31.8
547	26.0	25.8	24.7	27.0
548	26.3	27.8	26.7	28.5
549	27.0	30.0	26.3	28.8
550	29.7	31.3	30.3	31.5
MEAN	26.2	27.6	26.0	27.8
S.D.	2.64	2.24	2.65	2.09
N	24	24	24	25

--: Data Unavailable

[a]Calculated daily food consumption for successive period intervals

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 218M GROUP: 3-M SEX: MALE
DOSE: 7.5(mg base/kg/day)

ANIMAL #	DAY -3[b]	DAY 1	DAY 5	DAY 8	DAY 12	DAY 15	DAY 19	DAY 22	DAY 26	DAY 29	DAY 36	DAY 40
551	26.0	27.7	24.5	22.3	25.3	24.0	25.3	25.0	26.5	24.7	25.0	27.3
552	23.8	25.7	24.5	23.3	24.3	24.7	24.5	24.0	24.5	23.7	22.7	24.8
553	28.5	26.7	22.0	23.7	26.0	26.0	26.5	27.7	30.5	28.3	30.3	31.3
554	24.5	23.7	23.0	19.0	22.5	20.3	21.8	22.0	23.3	21.7	21.7	24.3
555	27.3	24.3	23.8	22.0	24.8	24.0	25.3	24.7	27.3	25.7	25.0	26.0
556	26.0	23.0	21.8	20.7	24.8	23.7	24.8	24.3	26.0	23.7	22.3	25.5
557	23.5	22.7	22.3	19.7	26.8	23.7	24.5	23.3	25.5	23.0	25.3	25.8
558	27.0	25.7	23.0	21.3	24.3	23.0	23.5	24.0	25.8	23.7	23.3	24.8
559	24.0	24.7	21.5	20.7	22.3	20.7	21.5	22.3	22.8	19.0	23.3	25.0
560	23.5	26.7	22.8	22.7	26.0	22.3	21.5	24.0	21.8	29.0	--	--
561	26.8	25.7	22.3	21.7	26.3	26.3	26.0	22.7	25.5	22.3	23.7	25.8
562	27.5	26.3	25.3	25.3	28.0	27.3	29.0	29.7	31.5	30.7	27.7	33.3
563	24.8	27.3	24.8	22.3	24.0	24.7	26.3	26.7	27.8	25.7	23.0	28.5
564	26.8	27.0	22.8	23.0	25.8	24.7	25.3	26.0	25.8	25.3	26.0	29.0
565	24.0	29.7	22.3	21.3	27.5	26.0	23.3	28.7	26.0	29.3	28.3	29.5
566	27.0	26.3	24.5	24.3	27.8	24.7	25.8	25.3	26.5	26.0	24.0	26.5
567	26.5	25.7	24.3	23.0	27.8	26.7	28.0	28.0	28.8	26.7	27.7	30.0
568	29.0	31.7	26.5	24.0	25.8	23.0	26.3	25.0	27.5	25.0	24.0	27.5
569	28.0	27.0	23.5	22.0	26.0	25.3	26.3	25.0	26.5	25.7	24.0	27.8
570	26.5	24.7	22.5	23.7	26.0	23.3	27.3	27.7	27.8	28.7	27.3	31.0
571	26.0	26.0	22.3	22.3	25.0	24.7	24.8	25.3	25.5	25.0	26.0	26.5
572	26.8	27.3	19.5	24.7	26.0	26.3	26.0	25.7	27.5	27.0	27.3	29.0
573	25.5	22.7	20.5	21.0	25.0	24.7	26.0	26.3	28.5	25.7	26.7	28.3
574	28.8	27.0	23.3	23.3	25.0	25.7	27.5	29.7	30.8	28.3	--	--
575	25.0	26.3	22.0	22.0	25.5	24.0	25.8	24.0	26.3	24.7	25.3	27.3
MEAN	26.1	26.1	23.0	22.4	25.5	24.4	25.3	25.5	26.7	25.5	25.2	27.6
S.D.	1.65	2.03	1.54	1.52	1.45	1.71	1.90	2.15	2.32	2.65	2.20	2.35
N	25	25	25	25	25	25	25	25	25	25	23	23

--: Data Unavailable

[a]Calculated daily food consumption for successive period intervals
[b]Baseline is day -7

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 218M GROUP: 3-M SEX: MALE
DOSE: 7.5(mg base/kg/day)

ANIMAL #	DAY 43	DAY 47	DAY 50	DAY 54
551	26.3	28.8	26.7	29.5
552	25.3	26.3	26.0	27.0
553	30.0	32.8	30.3	33.5
554	23.7	23.5	22.7	24.3
555	24.3	27.8	26.3	29.8
556	24.3	26.5	25.7	26.5
557	24.3	25.8	24.3	26.5
558	24.0	26.8	25.0	25.8
559	22.0	24.8	23.7	25.3
560	--	--	--	--
561	24.3	25.5	25.0	28.0
562	31.0	34.0	30.0	33.0
563	25.7	27.5	23.0	27.3
564	27.3	30.3	27.7	25.3
565	32.7	31.5	28.3	32.5
566	25.3	28.0	25.7	28.3
567	29.0	31.0	30.7	30.0
568	29.3	29.5	26.7	29.0
569	26.7	29.8	28.3	26.8
570	28.7	32.0	26.3	28.5
571	25.7	26.3	24.7	26.5
572	27.3	28.3	26.7	27.3
573	26.7	28.5	27.3	28.8
574	--	--	--	29.3
575	24.0	28.0	27.3	29.5
MEAN	26.4	28.4	26.5	28.3
S.D.	2.66	2.66	2.16	2.40
N	23	23	23	24

--: Data Unavailable

[a]Calculated daily food consumption for successive period intervals

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ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 218M GROUP: 4-M SEX: MALE
DOSE: 18(mg base/kg/day)

ANIMAL #	DAY -3[b]	DAY 1	DAY 5	DAY 8	DAY 12	DAY 15	DAY 19	DAY 22	DAY 26	DAY 29	DAY 36	DAY 40
576	26.5	24.7	19.8	18.7	22.0	15.0	19.3	22.3	21.5	21.0	22.3	22.8
577	28.0	26.3	20.8	17.7	21.0	19.3	19.5	22.0	23.3	24.7	23.0	23.8
578	26.8	27.3	24.3	25.3	27.5	25.3	26.5	26.3	27.3	25.3	25.7	28.5
579	23.3	23.7	20.3	19.3	19.5	19.0	19.0	19.0	22.0	21.3	19.7	20.5
580	24.5	23.3	19.8	22.3	22.5	22.0	22.5	22.3	23.0	21.7	22.7	23.0
581	25.3	24.3	19.3	18.3	18.8	17.7	19.8	22.7	22.5	22.3	23.0	22.5
582	24.5	23.0	24.0	20.7	21.8	22.0	22.5	21.7	23.5	23.3	24.3	24.5
583	27.0	26.3	21.5	21.7	21.5	21.3	20.3	21.7	21.8	20.7	24.3	26.5
584	28.5	26.7	20.0	19.3	20.5	18.3	19.8	20.0	23.5	23.0	20.3	22.5
585	26.3	25.7	22.3	22.7	25.5	23.3	23.5	22.3	25.5	25.3	24.7	27.8
586	27.8	26.3	21.3	21.3	22.3	20.3	20.8	21.7	23.0	22.7	24.3	25.3
587	30.8	28.7	24.8	21.0	22.8	21.3	23.3	22.3	24.8	23.3	23.0	14.8
588	27.3	26.0	20.0	20.0	23.8	23.7	22.3	21.7	23.8	23.7	--	--
589	21.8	22.0	20.3	18.7	20.8	15.7	18.5	21.7	24.3	23.0	22.0	23.0
590	27.5	29.0	21.0	18.7	23.0	19.7	24.0	17.3	18.5	24.3	23.7	27.3
591	24.5	23.3	18.8	19.0	17.3	16.3	19.3	18.7	22.0	21.3	19.0	21.3
592	26.0	24.0	19.3	18.0	21.3	19.7	20.5	20.3	22.8	21.0	23.3	24.5
593	29.3	28.0	23.8	20.3	23.5	22.0	21.8	22.3	25.3	25.3	24.0	26.8
594	24.5	28.7	24.8	25.0	26.8	22.3	21.5	24.7	24.3	24.3	26.0	27.0
595	23.3	20.7	20.8	18.7	19.8	17.3	10.3	20.3	22.5	20.3	22.0	24.3
596	27.0	27.3	18.8	17.3	19.0	18.0	19.8	20.3	24.8	23.7	25.3	24.5
597	26.0	26.3	23.3	20.0	21.0	21.7	20.5	21.3	24.5	23.0	22.3	24.5
598	28.0	26.0	22.5	23.7	25.5	25.3	25.5	25.0	27.0	27.0	29.0	30.5
599	26.5	25.7	20.8	20.3	22.0	19.3	19.3	18.0	23.3	24.0	22.7	26.3
600	25.5	24.7	17.0	23.3	21.0	20.0	20.0	19.3	21.5	21.0	22.0	23.3
MEAN	26.3	25.5	21.2	20.5	22.0	20.2	20.8	21.4	23.5	23.1	23.3	24.4
S.D.	2.03	2.14	2.07	2.23	2.46	2.75	3.02	2.10	1.86	1.74	2.12	3.15
N	25	25	25	25	25	25	25	25	25	25	24	24

--: Data Unavailable

[a]Calculated daily food consumption for successive period intervals
[b]Baseline is day -7

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 218M GROUP: 4-M SEX: MALE
DOSE: 18 (mg base/kg/day)

ANIMAL #	DAY 43	DAY 47	DAY 50	DAY 54
576	21.3	23.0	22.7	24.8
577	25.0	27.3	26.3	27.3
578	28.7	29.0	27.7	29.3
579	20.3	22.0	21.3	23.3
580	21.3	25.0	23.7	25.0
581	22.3	25.0	26.3	23.8
582	24.3	24.5	23.0	25.5
583	25.0	26.0	25.0	25.3
584	22.7	24.8	22.7	25.5
585	25.3	28.5	25.3	27.0
586	24.7	26.5	24.0	26.3
587	22.7	25.8	23.7	27.3
588	--	--	--	30.3
589	19.3	24.3	24.0	24.5
590	25.7	28.8	25.0	27.8
591	19.3	22.3	21.3	23.0
592	22.7	24.5	24.0	24.5
593	26.0	27.8	27.7	27.3
594	26.3	27.8	23.7	25.3
595	24.3	26.3	21.7	26.3
596	24.7	26.3	24.0	26.0
597	23.3	25.5	26.3	26.0
598	29.3	10.4	--	17.6
599	24.3	26.3	24.7	24.3
600	20.0	20.0	23.3	21.3
MEAN	23.7	24.9	24.2	25.4
S.D.	2.65	3.80	1.80	2.54
N	24	24	23	25

--: Data Unavailable

[a]Calculated daily food consumption for successive period intervals

APPENDIX C

SPERM ASSESSMENT REPORT

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MALE REPRODUCTIVE ASSESSMENT REPORT

FOR

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

UIC/TRL STUDY NUMBER: 218

PREPARED FOR:

TOXICOLOGY RESEARCH LABORATORY (TRL)
UNIVERSITY OF ILLINOIS AT CHICAGO (UIC)
DEPARTMENT OF PHARMACOLOGY
1940 W. TAYLOR ST
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Male Reproductive Assessment Report

Oral Fertility and Early Embryonic Development Study of WR6026 Dihydrochloride in Rats

UIC/TRL Study Number: 218

QUALITY ASSURANCE STATEMENT

This male reproductive assessment project has been inspected and audited by the PAI Quality Assurance Unit (QAU) as required by the Good Laboratory Practice (GLP) regulations promulgated by the U.S. Food and Drug Administration and Environmental Protection Agency (EPA). The male reproductive assessment report is an accurate reflection of the recorded data. The following table is a record of the inspections/audits performed and reported by the QAU.

Date of Inspection	Phase Inspected	Date Findings Reported to Management/ Study Reproductive Toxicologist
10/30/96	Sperm Count Phase	11/01/96
11/20-21/96	Individual Animal Data and Supporting Documentation	11/21/96
11/20-21/96	Draft Male Reproductive Assessment Report	11/21/96
11/26/96	Second Draft Male Reproductive Assessment Report	11/26/96

Sharon E. Abel
Quality Assurance Specialist

November 26, 1996
Date

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ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

II. MATERIALS AND METHODS

A. Gross Necropsy

At study termination, the surviving male rats were euthanized by carbon dioxide asphyxiation. For all animals, the abdominal, thoracic and pelvic cavities were opened and the viscera examined. Any abnormalities were recorded. Both testes were retained in Bouins's Fixative and the left epididymis, both seminal vesicles and the prostate gland were saved in 10% neutral buffered formalin for possible future histopathological examination.

B. Organ Weights

The testes, epididymides, seminal vesicles and prostate were excised, trimmed and weighed. The brain was also weighed to provide relative organ weight comparisons.

C. Sperm Sample Collection

For motility assessment, the right vas deferens was removed and immediately placed in a petri dish containing 10 ml of a solution consisting of 1% Bovine Serum Albumin dissolved in Phosphate Buffered Saline. The solution was prewarmed to a temperature of approximately 38°C. A three minute period was allowed for the sperm to swim out.

The right epididymis was weighed and placed on dry ice. The frozen epididymides were transferred to Pathology Associates Int., Frederick, MD. and stored frozen at -70°C or lower until evaluated for total sperm count and morphology.

D. Sperm Motility Evaluation

Following the swim out period, a sperm sample was obtained using a 100 μm deep cannula. The cannula was immediately loaded into the prewarmed stage of the Hamilton Thorne IVOS automated sperm analyzer. Five fields were automatically selected by the analyzer and each motion image was recorded and stored on an optical disk. The images were subsequently analyzed and the percent motility determined for each animal.

E. Total Sperm Count Determination

Each frozen epididymis was removed from the freezer, thawed and the caudal section was trimmed, weighed and then minced. The cauda epididymis was then homogenized and the suspension was transferred to a plastic, conical tube and vortexed. A 100 μl sample was transferred to a vial containing a fluorescent dye which uniquely stains the head of the sperm. A sample of the stained sperm was placed into a 20 μm deep glass slide which was loaded into the analyzer. Twenty fields were automatically selected by the analyzer for each animal and total sperm counts determined. The counts were reported adjusted for caudal epididymal weight.

F. Sperm Morphology

Two Eosin stained slides were prepared from the minced caudal epididymal samples obtained from each animal. The slides were evaluated and a minimum of 200 sperm cells/animal were examined for morphological development.

G. Statistical Analyses

The means and standard deviations for the brain/organ weight ratios, sperm motility, total sperm count data and the percentage of morphologically abnormal sperm were calculated. The organ weight data were analyzed by one-way analysis of variance (ANOVA). If a significant F ratio was obtained ($p \leq 0.05$), Dunnett's test was used for pair-wise comparisons of each treated group to the vehicle control group.

Sperm motility, total sperm count and the percentage of morphologically abnormal sperm were compared across groups using the Kruskal-Wallis nonparametric ANOVA test. If a significant effect occurred ($p \leq 0.05$), the Wilcoxon (Mann-Whitney U) test was used for pair-wise comparisons of each treated group to the vehicle control group.

Statistical analyses of the organ weight and sperm evaluation data were performed by entering the values into validated SAS programs (SAS/STAT User's Guide, 1989) which reside on an IBM™ compatible computer.

III. RESULTS

A. Gross Necropsy Observations

Table 1 (Summary Data)
Appendix A (Individual Data)

No treatment-related gross lesions were observed. An incidental finding of discolored seminal vesicles was noted for one animal in the control group.

B. Organ Weight Data

Table 2 (Summary Data)
Appendicies B and C (Individual Data)

Seminal vesicles, prostate and testes weights were comparable between study groups. Epididymis weights relative to brain weight were significantly reduced at 7.5 and 18 mg base/kg/day as compared to the control group. The reductions were not dose-related and no apparent adverse effects were noted in other evaluated parameters.

C. Sperm Motility

Table 3 (Summary Data)
Appendix D (Individual Data)

No apparent treatment-related effects were observed for the sperm motility data. Group mean values were comparable between the study groups, ranging from 97.6% in the control group to 99.0% in the 18 mg base/kg/day group.

D. Total Sperm Count

Table 3 (Summary Data)
Appendix D (Individual Data)

The number of sperm/gram of cauda epididymis was comparable between the study groups. Mean values ranged from 825.6 to 873.2 million sperm/gram. No treatment-related differences were observed.

E. Sperm Morphology

Table 3 (Summary Data)
Appendix E (Individual Data)

A low incidence of head/tail abnormalities was observed for animals in each study group including the control. No treatment related differences were observed.

IV. DISCUSSION AND CONCLUSIONS

Oral administration of WR6026 Dihydrochloride did not produce internal gross lesions in males. Male reproductive parameters including mean percent motility, total sperm count and sperm morphology were not affected by treatment. A statistically significant reduction in group mean epididymis weight relative to brain weight was observed in the 7.5 and 18 mg base/kg/day groups. In the absence of any other adverse effects, this nondose-related finding were not considered biologically relevant. Therefore, the no-effect level for male reproductive toxicity was established at 18 mg base/kg/day.

_____ Date: _____

Michael D. Mercieca, B.S.
Reproductive Toxicologist

V. REFERENCES

SAS Institute Inc., SAS/STAT User's Guide, Version 6, Fourth Edition, Volume 2 Cary, NC:SAS Institute Inc., 1989. Vol. 2 p. 201-244 and p. 1195-1210.

TABLE 1

STUDY NO.: TRL 218

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY
OF WR6026 DIHYDROCHLORIDE IN RATS

SUMMARY OF GROSS NECROPSY OBSERVATIONS

GROUP:	1	2	3	4
DOSE LEVEL (MG BASE/KG/DAY):	0	3	7.5	18
NUMBER OF MALES NECROPSIED	25	25	24	25
NO ABNORMALITIES DETECTED	24	25	24	25
SEMINAL VESICLES				
-PIGMENTATION, RED/PURPLE, BILATERAL	1	0	0	0

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TABLE 2

Study No.: TRL 218

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY
OF WR6026 DIHYDROCHLORIDE IN RATS

SUMMARY OF ORGAN/BRAIN WEIGHT RATIOS

Group Level	(MG BASE/KG/DAY)	1 0	2 3	3 7.5	4 18
EPIDIDYMIS	MEAN	0.74	0.73	0.69*	0.68*
	SD	0.06	0.09	0.05	0.05
	N	25	25	24	25
SEMINAL VESICLES	MEAN	0.64	0.71	0.64	0.66
	SD	0.15	0.19	0.13	0.15
	N	25	25	24	25
PROSTATE	MEAN	0.34	0.34	0.33	0.31
	SD	0.09	0.09	0.07	0.05
	N	25	25	24	25
TESTES	MEAN	1.69	1.65	1.62	1.66
	SD	0.13	0.16	0.10	0.16
	N	25	25	24	25

* SIGNIFICANTLY DIFFERENT FROM CONTROL ($p \leq 0.05$).

TABLE 3

DRAFT

Study No.: TRL 218

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY
OF WR6026 DIHYDROCHLORIDE IN RATS

SUMMARY OF SPERM ANALYSIS PARAMETERS

PERCENT MOTILITY

Group		1	2	3	4
Level	(MG BASE/KG/DAY)	0	3	7.5	18
	Mean	97.6	97.8	98.1	99.0
	SD	3.8	4.5	2.2	0.9
	N	25	25	24	25

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL.

SPERM DENSITY (10^6 SPERM/GRAM TISSUE)

Group		1	2	3	4
Level	(MG BASE/KG/DAY)	0	3	7.5	18
	Mean	873.2	852.3[a]	825.6	841.4
	SD	255.8	290.0	293.3	271.3
	N	25	24	24	25

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL.
[a]DOES NOT INCLUDE ONE ANIMAL FOR WHICH THE EPIDIDYMIS WAS APPARENTLY DESSICATED DURING STORAGE IN THE -70° FREEZER.

SPERM MORPHOLOGY DATA (PERCENT ABNORMAL)

Group		1	2	3	4
Level	(MG BASE/KG/DAY)	0	3	7.5	18
	Mean	0.3	0.2	0.2	0.3
	SD	0.5	0.3	0.4	0.4
	N	25	25	24	25

MEAN AND STANDARD DEVIATIONS WERE CALCULATED USING THE TOTAL NUMBER OF ABNORMAL SPERM AS A PERCENTAGE OF THE NUMBER SPERM EXAMINED.
NONE SIGNIFICANTLY DIFFERENT FROM CONTROL.

APPENDIX A

STUDY NO.: TRL 218

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT
STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL GROSS NECROPSY OBSERVATIONS

GROUP 1: 0 MG BASE/KG/DAY (VEHICLE)

ANIMAL#	ORGAN	OBSERVATION
501		NO ABNORMALITIES DETECTED
502		NO ABNORMALITIES DETECTED
503		NO ABNORMALITIES DETECTED
504		NO ABNORMALITIES DETECTED
505		NO ABNORMALITIES DETECTED
506		NO ABNORMALITIES DETECTED
507		NO ABNORMALITIES DETECTED
508		NO ABNORMALITIES DETECTED
509		NO ABNORMALITIES DETECTED
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512		NO ABNORMALITIES DETECTED
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516		NO ABNORMALITIES DETECTED
517		NO ABNORMALITIES DETECTED
518		NO ABNORMALITIES DETECTED
519		NO ABNORMALITIES DETECTED
520		NO ABNORMALITIES DETECTED
521		NO ABNORMALITIES DETECTED
522		NO ABMORNALITIES DETECTED
523	SEMINAL VESICLES	PIGMENTATION, RED/PURPLE, BILATERAL
524		NO ABNORMALITIES DETECTED
525		NO ABNORMALITIES DETECTED

APPENDIX A

STUDY NO.: TRL 218

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT
STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL GROSS NECROPSY OBSERVATIONS

GROUP 2: 3 MG BASE/KG/DAY (WR6026 DIHYDROCHLORIDE)

ANIMAL#	ORGAN	OBSERVATION
526		NO ABNORMALITIES DETECTED
527		NO ABNORMALITIES DETECTED
528		NO ABNORMALITIES DETECTED
529		NO ABNORMALITIES DETECTED
530		NO ABNORMALITIES DETECTED
531		NO ABNORMALITIES DETECTED
532		NO ABMORMALITIES DETECTED
533		NO ABNORMALITIES DETECTED
534		NO ABNORMALITIES DETECTED
535		NO ABNORMALITIES DETECTED
536		NO ABNORMALITIES DETECTED
537		NO ABNORMALITIES DETECTED
538		NO ABNORMALITIES DETECTED
539		NO ABNORMALITIES DETECTED
540		NO ABNORMALITIES DETECTED
541		NO ABNORMALITIES DETECTED
542		NO ABNORMALITIES DETECTED
543		NO ABNORMALITIES DETECTED
544		NO ABNORMALITIES DETECTED
545		NO ABNORMALITIES DETECTED
546		NO ABNORMALITIES DETECTED
547		NO ABNORMALITIES DETECTED
548		NO ABNORMALITIES DETECTED
549		NO ABNORMALITIES DETECTED
550		NO ABNORMALITIES DETECTED

APPENDIX A

STUDY NO.: TRL 218

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT
STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL GROSS NECROPSY OBSERVATIONS

GROUP 3: 7.5 MG BASE/KG/DAY (WR6026 DIHYDROCHLORIDE)

ANIMAL#	ORGAN	OBSERVATION
551		NO ABNORMALITIES DETECTED
552		NO ABNORMALITIES DETECTED
553		NO ABNORMALITIES DETECTED
554		NO ABNORMALITIES DETECTED
555		NO ABNORMALITIES DETECTED
556		NO ABNORMALITIES DETECTED
557		NO ABMORMALITIES DETECTED
558		NO ABNORMALITIES DETECTED
559		NO ABNORMALITIES DETECTED
560		a
561		NO ABNORMALITIES DETECTED
562		NO ABNORMALITIES DETECTED
563		NO ABNORMALITIES DETECTED
564		NO ABNORMALITIES DETECTED
565		NO ABNORMALITIES DETECTED
566		NO ABNORMALITIES DETECTED
567		NO ABNORMALITIES DETECTED
568		NO ABNORMALITIES DETECTED
569		NO ABNORMALITIES DETECTED
570		NO ABNORMALITIES DETECTED
571		NO ABNORMALITIES DETECTED
572		NO ABNORMALITIES DETECTED
573		NO ABNORMALITIES DETECTED
574		NO ABNORMALITIES DETECTED
575		NO ABNORMALITIES DETECTED

*ANIMAL DIED PRIOR TO SCHEDULED SACRIFICE

APPENDIX A

STUDY NO.: TRL 218

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT
STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL GROSS NECROPSY OBSERVATIONS

GROUP 4: 18 MG BASE/KG/DAY (WR6026 DIHYDROCHLORIDE)

ANIMAL#	ORGAN	OBSERVATION
576		NO ABNORMALITIES DETECTED
577		NO ABNORMALITIES DETECTED
578		NO ABNORMALITIES DETECTED
579		NO ABNORMALITIES DETECTED
580		NO ABNORMALITIES DETECTED
581		NO ABNORMALITIES DETECTED
582		NO ABNORMALITIES DETECTED
583		NO ABNORMALITIES DETECTED
584		NO ABNORMALITIES DETECTED
585		NO ABNORMALITIES DETECTED
586		NO ABNORMALITIES DETECTED
587		NO ABNORMALITIES DETECTED
588		NO ABNORMALITIES DETECTED
589		NO ABNORMALITIES DETECTED
590		NO ABNORMALITIES DETECTED
591		NO ABNORMALITIES DETECTED
592		NO ABNORMALITIES DETECTED
593		NO ABNORMALITIES DETECTED
594		NO ABNORMALITIES DETECTED
595		NO ABNORMALITIES DETECTED
596		NO ABNORMALITIES DETECTED
597		NO ABNORMALITIES DETECTED
598		NO ABNORMALITIES DETECTED
599		NO ABNORMALITIES DETECTED
600		NO ABNORMALITIES DETECTED

APPENDIX B

DRAFT

Study No.: TRL 218

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY
OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL ORGAN WEIGHT DATA
(BRAIN, EPIDIDYMIS, PROSTATE, SEMINAL VESICLES AND TESTES)
(GRAMS)

Group: 1 0 MG BASE/KG/DAY (VEHICLE)

Animal No.	BRAIN	EPIDIDYMIS	PROSTATE	SEMINAL VESICLES	TESTES
501	2.13	1.28	0.70	1.04	2.96
502	2.04	1.37	0.59	2.10	3.58
503	2.22	1.68	0.95	1.71	3.96
504	2.15	1.70	0.67	1.29	3.81
505	2.12	1.57	0.84	1.10	3.94
506	2.19	1.77	0.62	1.33	3.72
507	2.29	1.70	1.25	1.16	3.62
508	2.01	1.44	0.66	1.24	3.74
509	2.26	1.54	0.67	1.60	3.66
510	2.14	1.41	0.50	1.46	3.44
511	2.26	1.53	0.50	1.34	3.77
512	2.11	1.56	0.54	1.41	3.72
513	1.97	1.46	0.56	1.15	3.69
514	2.18	1.60	0.48	1.53	3.64
515	2.26	1.85	0.67	1.49	3.71
516	2.05	1.53	0.83	1.12	3.21
517	2.19	1.53	0.78	1.21	3.36
518	2.16	1.52	0.52	1.77	3.50
519	2.11	1.39	0.82	0.89	3.31
520	2.19	1.81	0.87	0.94	3.58
521	1.97	1.51	1.00	0.98	3.11
522	2.23	1.78	0.69	1.82	4.09
523	2.01	1.59	0.67	1.08	3.54
524	2.02	1.63	1.09	2.00	3.73
525	2.07	1.81	0.66	1.35	3.78

APPENDIX B

Study No.: TRL 218

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY
OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL ORGAN WEIGHT DATA
(BRAIN, EPIDIDYMIS, PROSTATE, SEMINAL VESICLES AND TESTES)
(GRAMS)

Group: 2 3 MG BASE/KG/DAY (WR6026 DIHYDROCHLORIDE)

Animal No.	BRAIN	EPIDIDYMIS	PROSTATE	SEMINAL VESICLES	TESTES
526	2.18	1.87	0.57	1.50	4.34
527	2.25	1.68	0.72	1.64	3.50
528	2.26	1.38	0.94	1.33	3.68
529	2.08	1.45	0.66	1.52	3.39
530	2.34	1.58	0.54	1.24	3.36
531	2.07	1.38	0.55	1.57	3.38
532	2.13	1.43	0.75	1.94	3.35
533	2.15	1.51	0.90	1.21	2.97
534	2.12	1.55	0.57	1.51	3.69
535	2.15	1.84	0.70	2.12	3.77
536	2.06	1.61	0.46	1.83	4.01
537	1.96	1.65	0.70	1.28	3.72
538	2.12	1.50	0.69	2.00	3.27
539	2.02	1.31	0.68	1.17	3.48
540	2.24	1.52	0.66	1.90	3.46
541	2.31	1.55	0.63	1.24	3.73
542	2.21	1.40	0.64	1.29	3.20
543	2.05	1.38	0.60	1.10	3.46
544	2.00	1.79	0.92	0.98	3.53
545	2.12	1.39	0.52	1.56	3.10
546	2.23	1.56	1.00	1.29	3.33
547	1.81	1.68	0.94	2.05	3.45
548	2.31	1.54	0.77	1.44	3.65
549	2.27	1.58	1.28	0.94	3.57
550	2.10	1.85	0.90	2.26	3.70

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APPENDIX B

Study No.: TRL 218

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY
OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL ORGAN WEIGHT DATA
(BRAIN, EPIDIDYMIS, PROSTATE, SEMINAL VESICLES AND TESTES)
(GRAMS)

Group: 3 7.5 MG BASE/KG/DAY (WR6026 DIHYDROCHLORIDE)

Animal No.	BRAIN	EPIDIDYMIS	PROSTATE	SEMINAL VESICLES	TESTES
551	2.07	1.70	0.82	1.33	3.42
552	2.30	1.55	0.83	1.28	3.57
553	2.37	1.53	0.52	1.09	3.55
554	2.20	1.39	0.85	0.90	3.55
555	2.38	1.59	0.85	1.62	3.75
556	2.21	1.38	0.48	1.82	3.61
557	2.08	1.58	0.51	1.30	3.64
558	2.33	1.54	1.02	1.62	3.36
559	2.17	1.61	0.67	1.04	3.66
560 [a]					
561	2.22	1.49	0.61	1.55	3.83
562	2.25	1.56	0.97	1.19	3.68
563	2.24	1.47	0.81	1.07	3.46
564	2.36	1.60	0.73	1.36	3.74
565	2.25	1.56	0.77	0.99	3.86
566	2.02	1.40	0.65	1.48	3.55
567	2.19	1.60	0.62	1.81	3.57
568	2.17	1.41	0.47	1.34	3.10
569	2.43	1.43	1.01	1.86	3.66
570	2.28	1.63	0.74	1.37	3.72
571	2.19	1.58	0.64	1.27	3.93
572	2.20	1.65	0.92	1.55	3.66
573	2.34	1.76	0.77	1.65	3.70
574	2.05	1.42	0.61	1.60	3.37
575	2.02	1.44	0.67	1.80	3.41

[a]ANIMAL DIED PRIOR TO SCHEDULED SACRIFICE

DRAFT

APPENDIX B

Study No.: TRL 218

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY
OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL ORGAN WEIGHT DATA
(BRAIN, EPIDIDYMIS, PROSTATE, SEMINAL VESICLES AND TESTES)
(GRAMS)

Group: 4 18 MG BASE/KG/DAY (WR6026 DIHYDROCHLORIDE)

Animal No.	BRAIN	EPIDIDYMIS	PROSTATE	SEMINAL VESICLES	TESTES
576	2.17	1.39	0.81	1.71	3.62
577	2.23	1.56	0.76	2.14	3.60
578	2.12	1.54	0.74	1.07	3.66
579	2.02	1.48	0.64	1.11	3.48
580	2.00	1.54	0.53	1.48	4.33
581	2.06	1.41	0.62	1.63	3.63
582	2.06	1.53	0.50	1.40	3.30
583	2.05	1.33	0.86	1.17	3.09
584	2.16	1.32	0.65	0.98	3.24
585	2.20	1.48	0.53	1.30	3.52
586	2.07	1.42	0.59	1.33	3.75
587	2.13	1.58	0.81	1.21	4.00
588	2.21	1.53	0.81	1.59	3.31
589	2.03	1.48	0.49	0.97	2.99
590	2.17	1.52	0.75	1.57	3.52
591	2.02	1.32	0.60	1.58	3.51
592	2.18	1.39	0.57	1.88	3.24
593	2.11	1.47	0.77	1.80	3.30
594	2.30	1.61	0.66	0.97	3.77
595	2.21	1.28	0.57	1.13	3.23
596	2.09	1.48	0.80	1.25	3.94
597	2.11	1.42	0.53	1.94	3.47
598	2.41	1.58	0.65	1.64	3.72
599	2.17	1.34	0.59	1.23	3.56
600	2.17	1.41	0.50	1.04	3.65

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APPENDIX C

Study No.: TRL 218

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY
OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL ORGAN WEIGHT DATA
(RELATIVE TO BRAIN WEIGHT)

Group: 1 0 MG BASE/KG/DAY (VEHICLE)

Animal No.	BRAIN	EPIDIDYMIS	PROSTATE	SEMINAL VESICLES	TESTES
501	2.13	0.60	0.33	0.49	1.39
502	2.04	0.67	0.29	1.03	1.75
503	2.22	0.76	0.43	0.77	1.78
504	2.15	0.79	0.31	0.60	1.77
505	2.12	0.74	0.40	0.52	1.86
506	2.19	0.81	0.28	0.61	1.70
507	2.29	0.74	0.55	0.51	1.58
508	2.01	0.72	0.33	0.62	1.86
509	2.26	0.68	0.30	0.71	1.62
510	2.14	0.66	0.23	0.68	1.61
511	2.26	0.68	0.22	0.59	1.67
512	2.11	0.74	0.26	0.67	1.76
513	1.97	0.74	0.28	0.58	1.87
514	2.18	0.73	0.22	0.70	1.67
515	2.26	0.82	0.30	0.66	1.64
516	2.05	0.75	0.40	0.55	1.57
517	2.19	0.70	0.36	0.55	1.53
518	2.16	0.70	0.24	0.82	1.62
519	2.11	0.66	0.39	0.42	1.57
520	2.19	0.83	0.40	0.43	1.63
521	1.97	0.77	0.51	0.50	1.58
522	2.23	0.80	0.31	0.82	1.83
523	2.01	0.79	0.33	0.54	1.76
524	2.02	0.81	0.54	0.99	1.85
525	2.07	0.87	0.32	0.65	1.83

APPENDIX C DRAFT

Study No.: TRL 218

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY
OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL ORGAN WEIGHT DATA
(RELATIVE TO BRAIN WEIGHT)

Group: 2 3 MG BASE/KG/DAY (WR6026 DIHYDROCHLORIDE)

Animal No.	BRAIN	EPIDIDYMIS	PROSTATE	SEMINAL VESICLES	TESTES
526	2.18	0.86	0.26	0.69	1.99
527	2.25	0.75	0.32	0.73	1.56
528	2.26	0.61	0.42	0.59	1.63
529	2.08	0.70	0.32	0.73	1.63
530	2.34	0.68	0.23	0.53	1.44
531	2.07	0.67	0.27	0.76	1.63
532	2.13	0.67	0.35	0.91	1.57
533	2.15	0.70	0.42	0.56	1.38
534	2.12	0.73	0.27	0.71	1.74
535	2.15	0.86	0.33	0.99	1.75
536	2.06	0.78	0.22	0.89	1.95
537	1.96	0.84	0.36	0.65	1.90
538	2.12	0.71	0.33	0.94	1.54
539	2.02	0.65	0.34	0.58	1.72
540	2.24	0.68	0.29	0.85	1.54
541	2.31	0.67	0.27	0.54	1.61
542	2.21	0.63	0.29	0.58	1.45
543	2.05	0.67	0.29	0.54	1.69
544	2.00	0.90	0.46	0.49	1.76
545	2.12	0.66	0.25	0.74	1.46
546	2.23	0.70	0.45	0.58	1.49
547	1.81	0.93	0.52	1.13	1.91
548	2.31	0.67	0.33	0.62	1.58
549	2.27	0.70	0.56	0.41	1.57
550	2.10	0.88	0.43	1.08	1.76

APPENDIX C

Study No.: TRL 218

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY
OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL ORGAN WEIGHT DATA
(RELATIVE TO BRAIN WEIGHT)

Group: 3 7.5 MG BASE/KG/DAY (WR6026 DIHYDROCHLORIDE)

Animal No.	BRAIN	EPIDIDYMIS	PROSTATE	SEMINAL VESICLES	TESTES
551	2.07	0.82	0.40	0.64	1.65
552	2.30	0.67	0.36	0.56	1.55
553	2.37	0.65	0.22	0.46	1.50
554	2.20	0.63	0.39	0.41	1.61
555	2.38	0.67	0.36	0.68	1.58
556	2.21	0.62	0.22	0.82	1.63
557	2.08	0.76	0.25	0.62	1.75
558	2.33	0.66	0.44	0.70	1.44
559	2.17	0.74	0.31	0.48	1.69
560 [a]					
561	2.22	0.67	0.27	0.70	1.73
562	2.25	0.69	0.43	0.53	1.64
563	2.24	0.66	0.36	0.48	1.54
564	2.36	0.68	0.31	0.58	1.58
565	2.25	0.69	0.34	0.44	1.72
566	2.02	0.69	0.32	0.73	1.76
567	2.19	0.73	0.28	0.83	1.63
568	2.17	0.65	0.22	0.62	1.43
569	2.43	0.59	0.42	0.77	1.51
570	2.28	0.71	0.32	0.60	1.63
571	2.19	0.72	0.29	0.58	1.79
572	2.20	0.75	0.42	0.70	1.66
573	2.34	0.75	0.33	0.71	1.58
574	2.05	0.69	0.30	0.78	1.64
575	2.02	0.71	0.33	0.89	1.69

[a]ANIMAL DIED PRIOR TO SCHEDULED SACRIFICE

APPENDIX C

Study No.: TRL 218

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY
OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL ORGAN WEIGHT DATA
(RELATIVE TO BRAIN WEIGHT)

Group: 4 18 MG BASE/KG/DAY (WR6026 DIHYDROCHLORIDE)

Animal No.	BRAIN	EPIDIDYMIS	PROSTATE	SEMINAL VESICLES	TESTES
576	2.17	0.64	0.37	0.79	1.67
577	2.23	0.70	0.34	0.96	1.61
578	2.12	0.73	0.35	0.50	1.73
579	2.02	0.73	0.32	0.55	1.72
580	2.00	0.77	0.26	0.74	2.16
581	2.06	0.68	0.30	0.79	1.76
582	2.06	0.74	0.24	0.68	1.60
583	2.05	0.65	0.42	0.57	1.51
584	2.16	0.61	0.30	0.45	1.50
585	2.20	0.67	0.24	0.59	1.60
586	2.07	0.69	0.29	0.64	1.81
587	2.13	0.74	0.38	0.57	1.88
588	2.21	0.69	0.37	0.72	1.50
589	2.03	0.73	0.24	0.48	1.47
590	2.17	0.70	0.35	0.72	1.62
591	2.02	0.65	0.30	0.78	1.74
592	2.18	0.64	0.26	0.86	1.49
593	2.11	0.70	0.36	0.85	1.56
594	2.30	0.70	0.29	0.42	1.64
595	2.21	0.58	0.26	0.51	1.46
596	2.09	0.71	0.38	0.60	1.89
597	2.11	0.67	0.25	0.92	1.64
598	2.41	0.66	0.27	0.68	1.54
599	2.17	0.62	0.27	0.57	1.64
600	2.17	0.65	0.23	0.48	1.68

APPENDIX D

Study No.: TRL 218

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY
OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL SPERM MOTILITY AND TOTAL COUNT DATA

Group: 1 0 MG BASE/KG/DAY (VEHICLE)

Animal No.	% Motility	Total Count (million/gram)
501	93	1257.0
502	98	685.7
503	97	832.2
504	99	806.1
505	100	714.4
506	99	1199.9
507	97	938.1
508	81	1101.7
509	95	648.0
510	100	1121.9
511	99	881.6
512	100	850.2
513	99	1060.7
514	100	588.2
515	99	899.0
516	100	652.9
517	98	764.7
518	98	1172.9
519	97	983.5
520	99	788.5
521	98	1533.1
522	98	476.4
523	100	722.2
524	99	562.6
525	97	587.8

APPENDIX D

DRAFT

Study No.: TRL 218

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY
OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL SPERM MOTILITY AND TOTAL COUNT DATA

Group: 2 3 MG BASE/KG/DAY (WR6026 DIHYDROCHLORIDE)

Animal No.	% Motility	Total Count (million/gram)
526	99	1397.4
527	100	574.4
528	100	835.7
529	98	604.8
530	96	739.7
531	98	610.1
532	98	499.9
533	99	1061.5
534	98	678.8
535	100	1029.8
536	97	55.5[a]
537	99	951.4
538	100	749.6
539	99	555.4
540	78	512.4
541	99	450.9
542	100	694.3
543	100	1328.1
544	99	1198.7
545	100	1143.7
546	100	1247.1
547	100	671.1
548	98	823.8
549	99	1259.9
550	92	837.0

[a]Epididymis was apparently dessicated during storage in the -70° freezer, not included in calculation of the mean.

APPENDIX D

Study No.: TRL 218

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY
OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL SPERM MOTILITY AND TOTAL COUNT DATA

Group: 3 7.5 MG BASE/KG/DAY (WR6026 DIHYDROCHLORIDE)

Animal No.	% Motility	Total Count (million/gram)
551	100	740.5
552	98	730.2
553	99	560.7
554	98	567.0
555	93	745.7
556	96	810.0
557	100	548.5
558	100	775.7
559	100	723.2
560 [a]		
561	97	1276.9
562	98	624.8
563	93	788.9
564	99	941.6
565	99	830.1
566	96	541.5
567	100	597.8
568	97	1306.5
569	100	662.7
570	100	657.4
571	100	1349.9
572	96	1607.5
573	100	1139.3
574	100	664.1
575	96	623.8

[a]ANIMAL DIED PRIOR TO SCHEDULED SACRIFICE

APPENDIX D

Study No.: TRL 218

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY
OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL SPERM MOTILITY AND TOTAL COUNT DATA

Group: 4 18 MG BASE/KG/DAY (WR6026 DIHYDROCHLORIDE)

Animal No.	% Motility	Total Count (million/gram)
576	99	1031.7
577	99	994.2
578	98	675.7
579	99	1139.9
580	99	1046.9
581	100	452.3
582	100	1026.9
583	96	671.1
584	98	408.0
585	100	1110.8
586	98	1311.4
587	98	1406.6
588	99	301.8
589	100	683.7
590	99	708.7
591	100	981.2
592	99	684.6
593	100	887.1
594	98	1087.7
595	99	850.2
596	99	689.6
597	99	671.1
598	99	725.4
599	100	805.5
600	99	683.7

APPENDIX E

STUDY NO.: TRL 218

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY
OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL SPERM MORPHOLOGY DATA

GROUP: 1 0 MG BASE/KG/DAY (VEHICLE)

Animal No.	Normal	Head				Tail			
		Amorphous	Small	Enlarged	Double	Coiled	Bent	Double	Other
501	198	2	0	0	0	0	0	0	0
502	199	1	0	0	0	0	0	0	0
503	200	0	0	0	0	0	0	0	0
504	200	0	0	0	0	0	0	0	0
505	199	1	0	0	0	0	0	0	0
506	200	0	0	0	0	0	0	0	0
507	198	2	0	0	0	0	0	0	0
508	200	0	0	0	0	0	0	0	0
509	199	1	0	0	0	0	0	0	0
510	200	0	0	0	0	0	0	0	0
511	200	0	0	0	0	0	0	0	0
512	200	0	0	0	0	0	0	0	0
513	200	0	0	0	0	0	0	0	0
514	200	0	0	0	0	0	0	0	0
515	200	0	0	0	0	0	0	0	0
516	200	0	0	0	0	0	0	0	0
517	198	2	0	0	0	0	0	0	0
518	200	0	0	0	0	0	0	0	0
519	198	1	0	0	0	1	0	0	0
520	199	1	0	0	0	0	0	0	0
521	200	0	0	0	0	0	0	0	0
522	199	1	0	0	0	0	0	0	0
523	197	3	0	0	0	0	0	0	0
524	200	0	0	0	0	0	0	0	0
525	199	1	0	0	0	0	0	0	0

APPENDIX E

STUDY NO.: TRL 218

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY
OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL SPERM MORPHOLOGY DATA

GROUP: 2 3 MG BASE/KG/DAY (WR6026 DIHYDROCHLORIDE)

Animal No.	Normal	Head				Tail			
		Amorphous	Small	Enlarged	Double	Coiled	Bent	Double	Other
526	200	0	0	0	0	0	0	0	0
527	200	0	0	0	0	0	0	0	0
528	200	0	0	0	0	0	0	0	0
529	198	2	0	0	0	0	0	0	0
530	199	0	0	0	0	0	1	0	0
531	199	0	0	0	0	1	0	0	0
532	200	0	0	0	0	0	0	0	0
533	200	0	0	0	0	0	0	0	0
534	199	1	0	0	0	0	0	0	0
535	199	1	0	0	0	0	0	0	0
536	200	0	0	0	0	0	0	0	0
537	200	0	0	0	0	0	0	0	0
538	199	1	0	0	0	0	0	0	0
539	200	0	0	0	0	0	0	0	0
540	200	0	0	0	0	0	0	0	0
541	199	1	0	0	0	0	0	0	0
542	200	0	0	0	0	0	0	0	0
543	200	0	0	0	0	0	0	0	0
544	199	1	0	0	0	0	0	0	0
545	200	0	0	0	0	0	0	0	0
546	198	1	0	0	0	0	1	0	0
547	200	0	0	0	0	0	0	0	0
548	200	0	0	0	0	0	0	0	0
549	200	0	0	0	0	0	0	0	0
550	199	1	0	0	0	0	0	0	0

APPENDIX E

STUDY NO.: TRL 218

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY
OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL SPERM MORPHOLOGY DATA

GROUP: 3 7.5 MG BASE/KG/DAY (WR6026 DIHYDROCHLORIDE)

Animal No.	Normal	Head				Tail			
		Amorphous	Small	Enlarged	Double	Coiled	Bent	Double	Other
551	200	0	0	0	0	0	0	0	0
552	200	0	0	0	0	0	0	0	0
553	199	1	0	0	0	0	0	0	0
554	199	1	0	0	0	0	0	0	0
555	200	0	0	0	0	0	0	0	0
556	200	0	0	0	0	0	0	0	0
557	200	0	0	0	0	0	0	0	0
558	200	0	0	0	0	0	0	0	0
559	198	2	0	0	0	0	0	0	0
560 [a]									
561	199	0	0	0	0	0	1	0	0
562	198	2	0	0	0	0	0	0	0
563	200	0	0	0	0	0	0	0	0
564	199	0	0	0	0	0	1	0	0
565	200	0	0	0	0	0	0	0	0
566	200	0	0	0	0	0	0	0	0
567	198	2	0	0	0	0	0	0	0
568	200	0	0	0	0	0	0	0	0
569	200	0	0	0	0	0	0	0	0
570	200	0	0	0	0	0	0	0	0
571	200	0	0	0	0	0	0	0	0
572	200	0	0	0	0	0	0	0	0
573	199	1	0	0	0	0	0	0	0
574	200	0	0	0	0	0	0	0	0
575	200	0	0	0	0	0	0	0	0

[a]ANIMAL DIED PRIOR TO SCHEDULED SACRIFICE

APPENDIX E

STUDY NO.: TRL 218

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY
OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL SPERM MORPHOLOGY DATA

GROUP: 4 18 MG BASE/KG/DAY (WR6026 DIHYDROCHLORIDE)

Animal No.	Normal	Head				Tail			Other
		Amorphous	Small	Enlarged	Double	Coiled	Bent	Double	
576	199	1	0	0	0	0	0	0	0
577	200	0	0	0	0	0	0	0	0
578	199	1	0	0	0	0	0	0	0
579	198	2	0	0	0	0	0	0	0
580	198	1	0	0	0	0	1	0	0
581	200	0	0	0	0	0	0	0	0
582	200	0	0	0	0	0	0	0	0
583	199	1	0	0	0	0	0	0	0
584	200	0	0	0	0	0	0	0	0
585	200	0	0	0	0	0	0	0	0
586	200	0	0	0	0	0	0	0	0
587	199	1	0	0	0	0	0	0	0
588	199	1	0	0	0	0	0	0	0
589	197	3	0	0	0	0	0	0	0
590	200	0	0	0	0	0	0	0	0
591	200	0	0	0	0	0	0	0	0
592	200	0	0	0	0	0	0	0	0
593	199	1	0	0	0	0	0	0	0
594	200	0	0	0	0	0	0	0	0
595	199	0	0	0	0	0	1	0	0
596	200	0	0	0	0	0	0	0	0
597	200	0	0	0	0	0	0	0	0
598	199	0	0	0	0	0	1	0	0
599	200	0	0	0	0	0	0	0	0
600	200	0	0	0	0	0	0	0	0

APPENDIX D

INDIVIDUAL FEMALE DATA: PRECOHABITATION AND COHABITATION PHASES

- Individual Observations
- Individual Body Weights
- Individual Weight Gain
- Individual Daily Food Consumption

ORAL FERTILITY AND EARLY EMBRYONIC
DEVELOPMENT STUDY OF
WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL CLINICAL SIGNS

STUDY: 218F
DAY 1-DAY 15

GROUP: 1-F
DOSE: 0(mg base/kg/day)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
601	Normal			DAY 1-DAY 15
602	Normal			DAY 1-DAY 15
603	Normal			DAY 1-DAY 15
604	Normal			DAY 1-DAY 15
605	Normal			DAY 1-DAY 15
606	Normal			DAY 1-DAY 15
607	Normal			DAY 1-DAY 15
608	Normal			DAY 1-DAY 15
609	Normal			DAY 1-DAY 15
610	Normal			DAY 1-DAY 15
611	Normal			DAY 1-DAY 15
612	Normal			DAY 1-DAY 15
613	Normal			DAY 1-DAY 15
614	Normal			DAY 1-DAY 15
615	Normal			DAY 1-DAY 15
616	Normal			DAY 1-DAY 15
617	Dark Material Around Eyes			DAY 3
	Dark Material Around Nose			DAY 3
	Normal			DAY 1-DAY 2
	Normal			DAY 4-DAY 15

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL CLINICAL SIGNS

STUDY: 218F GROUP: 1-F SEX: FEMALE
DAY 1-DAY 15 DOSE: 0 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
618	Normal			DAY 1-DAY 15
619	Normal			DAY 1-DAY 15
620	Normal			DAY 1-DAY 15
621	Normal			DAY 1-DAY 15
622	Normal			DAY 1-DAY 15
623	Normal			DAY 1-DAY 15
624	Normal			DAY 1-DAY 15
625	Normal			DAY 1-DAY 15

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 218F GROUP: 2-F SEX: FEMALE
DAY 1-DAY 15 DOSE: 3(mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
626	Normal			DAY 1-DAY 15
627	Normal			DAY 1-DAY 15
628	Normal			DAY 1-DAY 15
629	Normal			DAY 1-DAY 15
630	Normal			DAY 1-DAY 15
631	Normal			DAY 1-DAY 15
632	Normal			DAY 1-DAY 15
633	Normal			DAY 1-DAY 15
634	Normal			DAY 1-DAY 15
635	Normal			DAY 1-DAY 15
636	Normal			DAY 1-DAY 15
637	Normal			DAY 1-DAY 15
638	Normal			DAY 1-DAY 15
639	Normal			DAY 1-DAY 15
640	Normal			DAY 1-DAY 15
641	Normal			DAY 1-DAY 15
642	Normal			DAY 1-DAY 15
643	Normal			DAY 1-DAY 15
644	Normal			DAY 1-DAY 15

ORAL FERTILITY AND EARLY EMBRYONIC
DEVELOPMENT STUDY OF
WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL CLINICAL SIGNS

STUDY: 218F
DAY 1-DAY 15

GROUP: 2-F
DOSE: 3 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
645	Normal			DAY 1-DAY 15
646	Normal			DAY 1-DAY 15
647	Normal			DAY 1-DAY 15
648	Normal			DAY 1-DAY 15
649	Normal			DAY 1-DAY 15
650	Normal			DAY 1-DAY 15

ORAL FERTILITY AND EARLY EMBRYONIC
DEVELOPMENT STUDY OF
WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL CLINICAL SIGNS

STUDY: 218F GROUP: 3-F SEX: FEMALE
DAY 1-DAY 15 DOSE: 7.5 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
651	Normal			DAY 1-DAY 15
652	Normal			DAY 1-DAY 15
653	Normal			DAY 1-DAY 15
654	Normal			DAY 1-DAY 15
655	Normal			DAY 1-DAY 15
656	Normal			DAY 1-DAY 15
657	Normal			DAY 1-DAY 15
658	Normal			DAY 1-DAY 15
659	Normal			DAY 1-DAY 15
660	Animal Found Dead			DAY 13
	Normal			DAY 1-DAY 12
661	Normal			DAY 1-DAY 15
662	Normal			DAY 1-DAY 15
663	Normal			DAY 1-DAY 15
664	Normal			DAY 1-DAY 15
665	Normal			DAY 1-DAY 15
666	Normal			DAY 1-DAY 15
667	Normal			DAY 1-DAY 15
668	Normal			DAY 1-DAY 15

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 218F
DAY 1-DAY 15

GROUP: 3-F
DOSE: 7.5 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
669	Normal			DAY 1-DAY 15
670	Normal			DAY 1-DAY 15
671	Normal			DAY 1-DAY 15
672	Normal			DAY 1-DAY 15
673	Normal			DAY 1-DAY 15
674	Normal			DAY 1-DAY 15
675	Normal			DAY 1-DAY 15

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 218F GROUP: 4-F SEX: FEMALE
DAY 1-DAY 15 DOSE: 18(mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
676	Blue Tongue			DAY 10-DAY 12
	Normal			DAY 1-DAY 9
	Normal			DAY 13-DAY 15
677	Blue Tongue			DAY 9
	Blue Tongue			DAY 14
	Normal			DAY 1-DAY 8
	Normal			DAY 10-DAY 13
	Normal			DAY 15
678	Blue Tongue			DAY 12
	Normal			DAY 1-DAY 11
	Normal			DAY 13-DAY 15
679	Blue Tongue			DAY 12
	Blue Tongue			DAY 15
	Normal			DAY 1-DAY 11
	Normal			DAY 13-DAY 14
680	Normal			DAY 1-DAY 15
681	Blue Tongue			DAY 7
	Blue Tongue			DAY 12
	Blue Tongue			DAY 15
	Normal			DAY 1-DAY 6
	Normal			DAY 8-DAY 11
	Normal			DAY 13-DAY 14
682	Blue Tongue			DAY 12
	Normal			DAY 1-DAY 11
	Normal			DAY 13-DAY 15
683	Normal			DAY 1-DAY 15
684	Blue Tongue			DAY 12
	Blue Tongue			DAY 15
	Normal			DAY 1-DAY 11
	Normal			DAY 13-DAY 14

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 218F GROUP: 4-F SEX: FEMALE
DAY 1-DAY 15 DOSE: 18(mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
685	Normal			DAY 1-DAY 15
686	Normal			DAY 1-DAY 15
687	Normal			DAY 1-DAY 15
688	Normal			DAY 1-DAY 15
689	Blue Tongue			DAY 7
	Blue Tongue			DAY 10-DAY 11
	Normal			DAY 1-DAY 6
	Normal			DAY 8-DAY 9
	Normal			DAY 12-DAY 15
690	Blue Tongue			DAY 7-DAY 9
	Blue Tongue			DAY 12
	Normal			DAY 1-DAY 6
	Normal			DAY 10-DAY 11
	Normal			DAY 13-DAY 15
691	Blue Tongue			DAY 7-DAY 8
	Normal			DAY 1-DAY 6
	Normal			DAY 9-DAY 15
692	Blue Tongue			DAY 13
	Normal			DAY 1-DAY 12
	Normal			DAY 14-DAY 15
693	Blue Tongue			DAY 7-DAY 8
	Blue Tongue			DAY 13
	Normal			DAY 1-DAY 6
	Normal			DAY 9-DAY 12
	Normal			DAY 14-DAY 15
694	Normal			DAY 1-DAY 15
695	Blue Tongue			DAY 10-DAY 11
	Normal			DAY 1-DAY 9
	Normal			DAY 12-DAY 15

ORAL FERTILITY AND EARLY EMBRYONIC
DEVELOPMENT STUDY OF
WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL CLINICAL SIGNS

STUDY: 218F GROUP: 4-F SEX: FEMALE
DAY 1-DAY 15 DOSE: 18 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
696	Normal			DAY 1-DAY 15
697	Normal			DAY 1-DAY 15
698	Blue Tongue			DAY 7-DAY 12
	Blue Tongue			DAY 14-DAY 15
	Normal			DAY 1-DAY 6
	Normal			DAY 13
699	Normal			DAY 1-DAY 15
700	Blue Tongue			DAY 15
	Normal			DAY 1-DAY 14

INCIDENCE OF OBSERVATIONS

STUDY: 218F SEX: FEMALE

PERIOD	DOSE:(mg base/kg/day) GROUP:	0 1-F	3 2-F	7.5 3-F	18 4-F
DAY 1					
	No. Observed	25	25	25	25
	Normal	25 100%	25 100%	25 100%	25 100%
DAY 2					
	No. Observed	25	25	25	25
	Normal	25 100%	25 100%	25 100%	25 100%
DAY 3					
	No. Observed	25	25	25	25
	Normal	24 96%	25 100%	25 100%	25 100%
	Dark Material Around Eyes	1 4%	0	0	0
	Dark Material Around Nose	1 4%	0	0	0
DAY 4					
	No. Observed	25	25	25	25
	Normal	25 100%	25 100%	25 100%	25 100%
DAY 5					
	No. Observed	25	25	25	25
	Normal	25 100%	25 100%	25 100%	25 100%
DAY 6					
	No. Observed	25	25	25	25
	Normal	25 100%	25 100%	25 100%	25 100%
DAY 7					
	No. Observed	25	25	25	25
	Normal	25 100%	25 100%	25 100%	19 76%
	Blue Tongue	0	0	0	6 24%
DAY 8					
	No. Observed	25	25	25	25
	Normal	25 100%	25 100%	25 100%	21 84%
	Blue Tongue	0	0	0	4 16%
DAY 9					
	No. Observed	25	25	25	25
	Normal	25 100%	25 100%	25 100%	22 88%
	Blue Tongue	0	0	0	3 12%

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INCIDENCE OF OBSERVATIONS

STUDY: 218F SEX: FEMALE

PERIOD	DOSE: (mg base/kg/day) GROUP:	0 1-F	3 2-F	7.5 3-F	18 4-F
DAY 10					
	No. Observed	25	25	25	25
	Normal	25 100%	25 100%	25 100%	21 84%
	Blue Tongue	0	0	0	4 16%
DAY 11					
	No. Observed	25	25	25	25
	Normal	25 100%	25 100%	25 100%	21 84%
	Blue Tongue	0	0	0	4 16%
DAY 12					
	No. Observed	25	25	25	25
	Normal	25 100%	25 100%	25 100%	17 68%
	Blue Tongue	0	0	0	8 32%
DAY 13					
	No. Observed	25	25	25	25
	Animal Found Dead	0	0	1 4%	0
	Normal	25 100%	25 100%	24 96%	23 92%
	Blue Tongue	0	0	0	2 8%
DAY 14					
	No. Observed	25	25	24	25
	Normal	25 100%	25 100%	24 100%	23 92%
	Blue Tongue	0	0	0	2 8%
DAY 15					
	No. Observed	25	25	24	25
	Normal	25 100%	25 100%	24 100%	20 80%
	Blue Tongue	0	0	0	5 20%
DAY 16					
	No. Observed	16	15	14	13
	Normal	16 100%	15 100%	14 100%	13 100%
DAY 17					
	No. Observed	10	11	8	6
	Normal	10 100%	11 100%	8 100%	6 100%
DAY 18					
	No. Observed	5	5	4	4
	Normal	5 100%	5 100%	4 100%	4 100%

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INCIDENCE OF OBSERVATIONS

STUDY: 218F SEX: FEMALE

PERIOD	DOSE:(mg base/kg/day) GROUP:	0 1-F	3 2-F	7.5 3-F	18 4-F
DAY 19					
No. Observed		3	2	1	1
Normal		3 100%	2 100%	1 100%	1 100%
DAY 20					
No. Observed		3	1	1	1
Normal		3 100%	1 100%	1 100%	1 100%
DAY 21					
No. Observed		3	1	1	1
Normal		3 100%	1 100%	1 100%	1 100%
DAY 22					
No. Observed		3	1	1	1
Normal		3 100%	1 100%	1 100%	1 100%
DAY 23					
No. Observed		3	1	1	1
Normal		3 100%	1 100%	1 100%	1 100%
DAY 24					
No. Observed		3	1	1	1
Normal		3 100%	1 100%	1 100%	1 100%
DAY 25					
No. Observed		3	1	1	1
Normal		3 100%	1 100%	1 100%	1 100%
DAY 26					
No. Observed		3	1	1	1
Normal		3 100%	1 100%	1 100%	1 100%
DAY 27					
No. Observed		3	1	1	1
Normal		3 100%	1 100%	1 100%	1 100%
DAY 28					
No. Observed		3	1	1	1
Normal		3 100%	1 100%	1 100%	1 100%

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INCIDENCE OF OBSERVATIONS

STUDY: 218F SEX: FEMALE

PERIOD	DOSE:(mg base/kg/day) GROUP:	0 1-F	3 2-F	7.5 3-F	18 4-F
DAY 29					
No. Observed		3	1	1	1
Normal		3 100%	1 100%	1 100%	1 100%
DAY 30					
No. Observed		3	1	1	1
Normal		3 100%	1 100%	1 100%	1 100%
DAY 31					
No. Observed		3	1	1	1
Normal		3 100%	1 100%	1 100%	1 100%
DAY 32					
No. Observed		3	1	1	1
Normal		3 100%	1 100%	1 100%	1 100%
DAY 33					
No. Observed		3	1	1	1
Normal		3 100%	1 100%	1 100%	1 100%
DAY 34					
No. Observed		3	1	1	1
Normal		1 33%	1 100%	0	0
Sacrificed		2 67%	0	1 100%	1 100%
DAY 35					
No. Observed		1	1	0	0
Normal		1 100%	1 100%	0	0
DAY 36					
No. Observed		1	1	0	0
Normal		1 100%	1 100%	0	0
DAY 37					
No. Observed		1	1	0	0
Normal		1 100%	1 100%	0	0
DAY 38					
No. Observed		1	1	0	0
Normal		1 100%	1 100%	0	0

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INCIDENCE OF OBSERVATIONS

STUDY: 218F SEX: FEMALE

PERIOD	DOSE:(mg base/kg/day) GROUP:	0 1-F	3 2-F	7.5 3-F	18 4-F
DAY 39					
No. Observed		1	1	0	0
Normal		1 100%	1 100%	0	0
DAY 40					
No. Observed		1	1	0	0
Normal		1 100%	1 100%	0	0
DAY 41					
No. Observed		1	1	0	0
Normal		1 100%	1 100%	0	0
DAY 42					
No. Observed		1	1	0	0
Normal		1 100%	1 100%	0	0
DAY 43					
No. Observed		1	1	0	0
Normal		1 100%	1 100%	0	0
DAY 44					
No. Observed		1	1	0	0
Normal		1 100%	1 100%	0	0
DAY 45					
No. Observed		1	1	0	0
Normal		1 100%	1 100%	0	0
DAY 46					
No. Observed		1	1	0	0
Sacrificed		1 100%	1 100%	0	0

DRAFT

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 218F GROUP: 1-F SEX: FEMALE
DOSE: 0 (mg base/kg/day)

ANIMAL #	DAY -3	DAY 1	DAY 5	DAY 8	DAY 12	DAY 15
601	230	234	242	240	248	258
602	229	224	228	234	240	245
603	232	231	244	239	244	253
604	233	240	248	251	254	255
605	209	222	231	226	241	247
606	239	239	244	243	249	260
607	244	249	259	260	269	274
608	206	208	219	222	229	234
609	216	214	215	212	215	221
610	220	225	228	233	238	237
611	220	223	219	231	233	242
612	221	232	238	246	252	255
613	226	228	235	237	240	241
614	216	228	226	229	245	253
615	218	237	236	241	249	252
616	214	226	230	232	243	251
617	227	228	199	213	230	243
618	210	219	222	227	234	233
619	232	234	242	248	257	266
620	212	207	204	200	211	222
621	219	219	225	230	236	243
622	246	254	265	267	281	278
623	223	222	228	232	238	244
624	200	197	198	194	198	206
625	225	234	241	244	250	253
MEAN	223	227	231	233	241	247
S.D.	11.4	12.7	16.5	16.7	17.2	16.0
N	25	25	25	25	25	25

--: Data Unavailable

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 218F GROUP: 2-F SEX: FEMALE
DOSE: 3 (mg base/kg/day)

ANIMAL #	DAY -3	DAY 1	DAY 5	DAY 8	DAY 12	DAY 15
626	228	224	233	236	244	243
627	206	205	233	241	246	249
628	227	233	243	236	251	252
629	220	215	224	219	227	231
630	228	228	237	234	240	248
631	219	217	222	225	231	232
632	221	225	223	229	237	242
633	230	233	239	237	240	247
634	218	217	217	215	216	210
635	213	215	220	225	233	231
636	220	221	216	225	228	232
637	202	208	202	206	214	206
638	237	243	239	248	252	254
639	237	244	246	226	255	263
640	232	227	229	231	242	247
641	240	248	247	248	256	267
642	210	213	214	222	228	220
643	230	235	245	245	256	266
644	209	216	223	213	219	229
645	223	238	244	244	257	265
646	215	221	225	230	237	234
647	225	225	228	238	239	238
648	247	247	259	265	279	277
649	210	217	225	231	232	243
650	216	224	232	234	247	248
MEAN	223	226	231	232	240	243
S.D.	11.3	12.0	12.8	12.7	14.8	17.4
N	25	25	25	25	25	25

--: Data Unavailable

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 218F GROUP: 3-F SEX: FEMALE
DOSE: 7.5 (mg base/kg/day)

ANIMAL #	DAY -3	DAY 1	DAY 5	DAY 8	DAY 12	DAY 15
651	220	217	223	217	223	224
652	217	220	225	233	243	246
653	222	222	229	229	232	231
654	232	234	234	231	233	239
655	210	214	217	215	218	213
656	248	249	255	268	273	279
657	218	216	222	222	226	229
658	208	209	200	203	209	215
659	239	249	250	251	263	274
660	242	247	254	254	268	c
661	219	224	223	222	230	227
662	227	232	236	235	245	254
663	225	230	230	223	228	239
664	212	212	217	216	220	207
665	200	212	211	217	220	221
666	229	231	238	243	249	254
667	224	231	238	239	242	248
668	236	242	248	252	261	260
669	209	216	222	221	229	226
670	228	234	239	241	251	249
671	234	237	226	247	250	254
672	220	221	216	222	225	221
673	231	230	239	244	244	247
674	216	226	227	228	240	245
675	214	225	232	235	242	244
MEAN	223	227	230	232	239	239
S.D.	11.6	11.7	13.5	15.2	16.6	18.6
N	25	25	25	25	25	24

--: Data Unavailable c: Animal Found Dead

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

DRAFT

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 218F GROUP: 4-F SEX: FEMALE
DOSE: 18 (mg base/kg/day)

ANIMAL #	DAY -3	DAY 1	DAY 5	DAY 8	DAY 12	DAY 15
676	234	233	239	241	240	251
677	207	210	211	215	211	217
678	244	244	240	236	246	246
679	213	215	216	215	217	221
680	211	208	205	210	214	224
681	210	208	209	217	215	219
682	232	241	243	243	242	241
683	232	240	239	238	252	267
684	205	210	208	203	209	220
685	228	225	230	234	238	243
686	237	244	246	243	252	251
687	227	227	229	234	236	239
688	218	222	219	222	236	237
689	223	230	219	228	227	231
690	217	224	220	220	227	236
691	220	223	230	226	237	240
692	227	233	232	234	242	246
693	219	217	221	218	220	221
694	243	246	257	262	271	281
695	219	217	218	222	221	226
696	221	227	224	215	225	229
697	208	206	207	203	210	208
698	215	224	226	222	229	229
699	223	236	233	238	243	247
700	229	223	225	233	238	243
MEAN	222	225	226	227	232	237
S.D.	10.8	12.2	13.4	13.9	15.4	16.3
N	25	25	25	25	25	25

--: Data Unavailable

DRAFT

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 218F GROUP: 1-F SEX: FEMALE
DOSE: 0 (mg base/kg/day)

ANIMAL #	DAY 5[b]	DAY 8	DAY 12	DAY 15	TOTAL GAIN
601	8	-2	8	10	24
602	4	6	6	5	21
603	13	-5	5	9	22
604	8	3	3	1	15
605	9	-5	15	6	25
606	5	-1	6	11	21
607	10	1	9	5	25
608	11	3	7	5	26
609	1	-3	3	6	7
610	3	5	5	-1	12
611	-4	12	2	9	19
612	6	8	6	3	23
613	7	2	3	1	13
614	-2	3	16	8	25
615	-1	5	8	3	15
616	4	2	11	8	25
617	-29	14	17	13	15
618	3	5	7	-1	14
619	8	6	9	9	32
620	-3	-4	11	11	15
621	6	5	6	7	24
622	11	2	14	-3	24
623	6	4	6	6	22
624	1	-4	4	8	9
625	7	3	6	3	19
MEAN	4	3	8	6	20
S.D.	8.2	4.9	4.2	4.1	6.1
N	25	25	25	25	25

--: Data Unavailable

[a]Weight gains compared to the previous period
[b]Baseline is day 1

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 218F GROUP: 2-F SEX: FEMALE
DOSE: 3 (mg base/kg/day)

ANIMAL #	DAY 5[b]	DAY 8	DAY 12	DAY 15	TOTAL GAIN
626	9	3	8	-1	19
627	28	8	5	3	44
628	10	-7	15	1	19
629	9	-5	8	4	16
630	9	-3	6	8	20
631	5	3	6	1	15
632	-2	6	8	5	17
633	6	-2	3	7	14
634	0	-2	1	-6	-7
635	5	5	8	-2	16
636	-5	9	3	4	11
637	-6	4	8	-8	-2
638	-4	9	4	2	11
639	2	-20	29	8	19
640	2	2	11	5	20
641	-1	1	8	11	19
642	1	8	6	-8	7
643	10	0	11	10	31
644	7	-10	6	10	13
645	6	0	13	8	27
646	4	5	7	-3	13
647	3	10	1	-1	13
648	12	6	14	-2	30
649	8	6	1	11	26
650	8	2	13	1	24
MEAN	5	2	8	3	17
S.D.	6.9	6.8	5.9	5.7	10.3
N	25	25	25	25	25

--: Data Unavailable

[a]Weight gains compared to the previous period
[b]Baseline is day 1

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 218F GROUP: 3-F SEX: FEMALE
DOSE: 7.5(mg base/kg/day)

ANIMAL #	DAY 5[b]	DAY 8	DAY 12	DAY 15	TOTAL GAIN
651	6	-6	6	1	7
652	5	8	10	3	26
653	7	0	3	-1	9
654	0	-3	2	6	5
655	3	-2	3	-5	-1
656	6	13	5	6	30
657	6	0	4	3	13
658	-9	3	6	6	6
659	1	1	12	11	25
660	7	0	14	c	--
661	-1	-1	8	-3	3
662	4	-1	10	9	22
663	0	-7	5	11	9
664	5	-1	4	-13	-5
665	-1	6	3	1	9
666	7	5	6	5	23
667	7	1	3	6	17
668	6	4	9	-1	18
669	6	-1	8	-3	10
670	5	2	10	-2	15
671	-11	21	3	4	17
672	-5	6	3	-4	0
673	9	5	0	3	17
674	1	1	12	5	19
675	7	3	7	2	19
MEAN	3	2	6	2	13
S.D.	5.1	5.8	3.6	5.5	9.2
N	25	25	25	24	24

--: Data Unavailable c: Animal Found Dead

[a]Weight gains compared to the previous period
[b]Baseline is day 1

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

DRAFT

INDIVIDUAL WEIGHT GAIN (Grams) [a]

STUDY: 218F GROUP: 4-F SEX: FEMALE
DOSE: 18 (mg base/kg/day)

ANIMAL #	DAY 5 [b]	DAY 8	DAY 12	DAY 15	TOTAL GAIN
676	6	2	-1	11	18
677	1	4	-4	6	7
678	-4	-4	10	0	2
679	1	-1	2	4	6
680	-3	5	4	10	16
681	1	8	-2	4	11
682	2	0	-1	-1	0
683	-1	-1	14	15	27
684	-2	-5	6	11	10
685	5	4	4	5	18
686	2	-3	9	-1	7
687	2	5	2	3	12
688	-3	3	14	1	15
689	-11	9	-1	4	1
690	-4	0	7	9	12
691	7	-4	11	3	17
692	-1	2	8	4	13
693	4	-3	2	1	4
694	11	5	9	10	35
695	1	4	-1	5	9
696	-3	-9	10	4	2
697	1	-4	7	-2	2
698	2	-4	7	0	5
699	-3	5	5	4	11
700	2	8	5	5	20
MEAN	1	1	5	5	11
S.D.	4.4	4.7	5.0	4.3	8.4
N	25	25	25	25	25

--: Data Unavailable

[a] Weight gains compared to the previous period
[b] Baseline is day 1

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 218F GROUP: 1-F SEX: FEMALE
DOSE: 0 (mg base/kg/day)

ANIMAL #	DAY -3[b]	DAY 1	DAY 5	DAY 8	DAY 12	DAY 15
601	18.5	16.3	18.0	15.7	17.3	16.0
602	17.8	14.0	15.5	16.7	16.0	14.0
603	16.8	15.3	17.0	16.0	17.3	16.7
604	19.5	16.3	17.8	17.3	17.8	16.3
605	17.3	17.7	17.3	15.7	18.8	16.7
606	20.3	16.3	17.3	17.7	19.0	20.0
607	18.5	22.0	25.5	19.7	27.3	22.3
608	16.3	15.0	16.0	15.3	16.0	14.7
609	17.3	13.3	15.0	14.3	15.3	15.3
610	18.3	14.0	13.5	14.7	16.3	16.3
611	15.8	15.3	16.0	17.3	16.5	16.3
612	16.5	17.3	17.3	17.3	18.3	15.3
613	16.3	14.0	16.8	15.0	17.0	15.3
614	17.3	16.0	13.8	15.3	17.5	17.3
615	18.0	18.0	16.5	17.0	18.5	16.3
616	16.0	15.3	14.0	17.0	15.3	21.3
617	32.3	14.7	2.3	14.0	15.5	16.0
618	16.0	15.7	16.0	16.0	16.8	15.0
619	20.0	16.7	18.5	--	18.0	17.3
620	16.8	13.7	13.3	14.0	15.5	17.7
621	17.5	15.3	16.0	17.7	16.5	16.0
622	19.0	17.0	18.0	16.0	22.8	16.0
623	17.3	15.3	17.5	18.0	18.3	16.0
624	15.8	12.7	13.3	13.7	15.5	16.0
625	16.8	17.0	17.0	15.7	17.5	14.3
MEAN	18.1	15.8	16.0	16.1	17.6	16.6
S.D.	3.23	1.90	3.74	1.49	2.59	1.98
N	25	25	25	24	25	25

--: Data Unavailable

[a]Calculated daily food consumption for successive period intervals
[b]Baseline is day -7

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 218F GROUP: 2-F SEX: FEMALE
DOSE: 3 (mg base/kg/day)

ANIMAL #	DAY -3[b]	DAY 1	DAY 5	DAY 8	DAY 12	DAY 15
626	17.3	15.0	15.0	16.3	17.5	15.0
627	15.8	18.0	14.5	17.0	16.0	15.0
628	16.8	--	20.0	18.0	19.0	17.7
629	18.0	14.3	16.3	15.7	17.3	15.7
630	19.3	16.7	16.3	17.0	18.0	17.0
631	16.5	16.0	14.8	17.7	17.0	15.0
632	16.3	16.3	13.5	16.3	18.5	15.7
633	17.5	17.7	17.3	17.0	18.3	16.7
634	17.3	15.0	14.5	14.0	14.3	14.7
635	16.0	15.7	15.0	16.0	16.5	14.0
636	17.5	15.7	14.8	16.3	17.8	15.3
637	15.5	13.0	11.8	14.0	14.0	11.0
638	17.5	14.7	14.5	15.7	14.8	16.7
639	18.3	15.3	15.8	13.3	17.0	19.7
640	18.0	14.3	15.3	16.0	17.5	16.3
641	17.5	15.7	15.5	16.3	17.3	21.7
642	14.8	13.3	14.8	15.7	15.3	13.3
643	18.5	16.0	16.3	16.7	18.0	19.7
644	23.8	14.3	13.5	15.7	13.3	13.0
645	17.0	18.0	15.8	15.0	18.3	16.3
646	17.5	17.7	16.0	16.3	15.8	14.7
647	15.3	14.7	14.3	14.7	13.8	13.7
648	19.8	16.7	18.3	17.7	19.5	20.0
649	16.8	15.7	15.0	15.3	17.8	16.7
650	16.8	17.0	16.5	16.3	18.0	16.7
MEAN	17.4	15.7	15.4	16.0	16.8	16.1
S.D.	1.78	1.40	1.62	1.17	1.72	2.41
N	25	24	25	25	25	25

--: Data Unavailable

[a]Calculated daily food consumption for successive period intervals
[b]Baseline is day -7

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 218F GROUP: 3-F SEX: FEMALE
DOSE: 7.5(mg base/kg/day)

ANIMAL #	DAY -3[b]	DAY 1	DAY 5	DAY 8	DAY 12	DAY 15
651	15.5	15.3	15.5	12.7	14.5	13.7
652	17.8	15.3	14.8	17.0	17.0	15.7
653	17.5	16.0	17.0	14.7	16.0	14.3
654	17.5	16.0	13.5	15.0	14.8	14.7
655	15.0	13.7	12.5	11.3	13.5	10.7
656	19.0	17.7	17.0	17.0	17.3	15.3
657	17.5	14.3	15.8	14.0	14.8	13.7
658	15.3	14.0	12.0	11.3	14.0	13.7
659	19.5	16.7	15.8	14.3	18.0	17.7
660	19.8	17.0	18.0	15.7	18.3	c
661	16.3	14.7	12.8	12.3	14.3	13.3
662	17.8	16.3	15.3	14.3	17.0	15.3
663	18.0	16.7	15.3	13.0	16.5	16.3
664	15.5	13.7	13.3	12.7	14.0	12.7
665	17.0	17.3	15.3	15.3	17.8	13.7
666	18.3	17.3	16.3	15.7	18.0	17.0
667	17.3	16.7	14.5	13.7	14.5	13.7
668	20.5	18.3	17.8	16.3	18.0	17.0
669	15.3	16.0	14.3	13.3	15.8	14.0
670	18.5	17.7	16.5	14.7	16.0	14.7
671	20.3	18.0	15.0	19.0	17.8	16.0
672	16.3	15.7	11.8	14.3	13.5	11.7
673	16.8	16.0	15.3	16.0	15.0	12.7
674	21.3	17.7	16.0	17.0	19.3	15.7
675	16.3	16.7	15.0	14.0	15.5	13.7
MEAN	17.6	16.2	15.1	14.6	16.0	14.5
S.D.	1.75	1.35	1.68	1.88	1.72	1.70
N	25	25	25	25	25	24

--: Data Unavailable c: Animal Found Dead

[a]Calculated daily food consumption for successive period intervals
[b]Baseline is day -7

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 218F GROUP: 4-F SEX: FEMALE
DOSE: 18 (mg base/kg/day)

ANIMAL #	DAY -3[b]	DAY 1	DAY 5	DAY 8	DAY 12	DAY 15
676	18.3	15.7	15.8	16.3	17.0	16.3
677	17.0	14.3	11.8	11.0	10.8	11.7
678	17.8	16.0	11.8	11.0	14.0	12.3
679	16.8	16.0	12.8	13.3	12.8	12.7
680	15.0	13.3	11.0	11.7	12.0	11.7
681	19.3	15.3	15.3	15.7	13.8	13.7
682	16.0	16.7	13.3	12.0	11.8	12.0
683	19.3	17.0	14.5	14.7	17.5	17.0
684	15.5	14.7	12.0	13.3	13.5	14.3
685	19.5	17.3	16.3	7.3	18.8	16.0
686	17.3	18.7	14.5	14.0	16.5	12.7
687	18.0	16.0	14.8	16.0	15.0	13.0
688	19.8	16.3	14.3	17.0	16.5	14.3
689	19.3	19.0	11.3	10.7	10.8	12.0
690	17.3	17.7	13.5	10.3	13.3	13.3
691	17.5	15.3	20.5	12.0	13.5	14.3
692	16.5	15.7	13.8	14.3	14.8	12.7
693	13.3	12.0	10.8	15.3	11.5	13.0
694	20.3	19.0	19.0	17.3	18.8	17.7
695	18.0	16.0	13.5	14.7	14.0	13.3
696	14.5	17.0	10.5	8.7	12.0	12.0
697	14.3	12.7	11.5	10.0	12.0	10.7
698	15.5	15.7	12.8	9.7	11.3	11.0
699	17.8	18.0	15.0	14.0	17.0	17.3
700	18.0	16.0	13.3	14.0	13.5	13.3
MEAN	17.3	16.1	13.7	13.0	14.1	13.5
S.D.	1.85	1.78	2.43	2.68	2.45	1.95
N	25	25	25	25	25	25

--: Data Unavailable

[a]Calculated daily food consumption for successive period intervals
[b]Baseline is day -7

APPENDIX E

INDIVIDUAL FEMALE DATA: GESTATION PHASE

- Individual Observations
- Individual Body Weights
- Individual Weight Gain
- Individual Daily Food Consumption

ORAL FERTILITY AND EARLY EMBRYONIC
DEVELOPMENT STUDY OF WR6026
DIHYDROCHLORIDE IN RATS

INDIVIDUAL CLINICAL SIGNS

STUDY: 218 GROUP: 1-F SEX: FEMALE
GD 0-GD 20 DOSE: 0 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
601	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
602	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
603	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
604	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
606	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
608	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
609	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
610	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
611	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
612	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
613	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
614	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
615	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

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INDIVIDUAL CLINICAL SIGNS

STUDY: 218 GROUP: 1-F SEX: FEMALE
GD 0-GD 20 DOSE: 0(mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
616	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
617	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
618	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
619	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
620	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
621	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
622	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
624	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
625	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16

ORAL FERTILITY AND EARLY EMBRYONIC
DEVELOPMENT STUDY OF WR6026
DIHYDROCHLORIDE IN RATS

INDIVIDUAL CLINICAL SIGNS

STUDY: 218 GROUP: 2-F SEX: FEMALE
GD 0-GD 20 DOSE: 3 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
626	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
627	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
628	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
630	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
631	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
632	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
633	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
634	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
635	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
636	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
637	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
638	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
639	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

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INDIVIDUAL CLINICAL SIGNS

STUDY: 218 GROUP: 2-F SEX: FEMALE
GD 0-GD 20 DOSE: 3 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
640	Normal Scheduled Sacrifice			GD 0-GD 15 GD 16
641	Normal Scheduled Sacrifice			GD 0-GD 15 GD 16
642	Normal Scheduled Sacrifice			GD 0-GD 15 GD 16
643	Normal Scheduled Sacrifice			GD 0-GD 15 GD 16
644	Normal Scheduled Sacrifice			GD 0-GD 15 GD 16
645	Normal Scheduled Sacrifice			GD 0-GD 15 GD 16
646	Normal Scheduled Sacrifice			GD 0-GD 15 GD 16
647[a]	Normal Scheduled Sacrifice			GD 0-GD 16 GD 17
648	Normal Scheduled Sacrifice			GD 0-GD 15 GD 16
649	Normal Scheduled Sacrifice			GD 0-GD 15 GD 16
650	Normal Scheduled Sacrifice			GD 0-GD 15 GD 16

[a]Animal No. 647 was inadvertently sacrificed on gestation day 17. This animals was correctly dosed throughout the precohabitation and cohabitation phases as well as from gestation days 0 - 6.

ORAL FERTILITY AND EARLY EMBRYONIC
DEVELOPMENT STUDY OF WR6026
DIHYDROCHLORIDE IN RATS

INDIVIDUAL CLINICAL SIGNS

STUDY: 218 GROUP: 3-F SEX: FEMALE
GD 0-GD 20 DOSE: 7.5(mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
651	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
652	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
653	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
654	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
655	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
656	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
657	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
658	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
659	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
661	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
662	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
663	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
664	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL CLINICAL SIGNS

STUDY: 218 GROUP: 3-F SEX: FEMALE
GD 0-GD 20 DOSE: 7.5 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
665	Normal Scheduled Sacrifice			GD 0-GD 15 GD 16
666	Normal Scheduled Sacrifice			GD 0-GD 15 GD 16
667	Normal Scheduled Sacrifice			GD 0-GD 15 GD 16
668	Normal Scheduled Sacrifice			GD 0-GD 15 GD 16
669	Normal Scheduled Sacrifice			GD 0-GD 15 GD 16
670	Normal Scheduled Sacrifice			GD 0-GD 15 GD 16
671	Normal Scheduled Sacrifice			GD 0-GD 15 GD 16
672	Normal Scheduled Sacrifice			GD 0-GD 15 GD 16
673	Normal Scheduled Sacrifice			GD 0-GD 15 GD 16
675	Normal Scheduled Sacrifice			GD 0-GD 15 GD 16

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ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL CLINICAL SIGNS

STUDY: 218 GROUP: 4-F SEX: FEMALE
GD 0-GD 20 DOSE: 18 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
676	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
677	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
678	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
679	Blue Tongue			GD 2
	Normal			GD 0-GD 1
	Normal			GD 3-GD 15
	Scheduled Sacrifice			GD 16
680	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
681	Blue Tongue			GD 3
	Blue Tongue			GD 6
	Normal			GD 0-GD 2
	Normal			GD 4-GD 5
	Normal			GD 7-GD 15
	Scheduled Sacrifice			GD 16
682	Blue Tongue			GD 4
	Normal			GD 0-GD 3
	Normal			GD 5-GD 15
	Scheduled Sacrifice			GD 16
683	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
684	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
685	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL CLINICAL SIGNS

STUDY: 218 GROUP: 4-F SEX: FEMALE
GD 0-GD 20 DOSE: 18 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
686	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
687	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
689	Blue Tongue			GD 3
	Normal			GD 0-GD 2
	Normal			GD 4-GD 15
	Scheduled Sacrifice			GD 16
690	Blue Tongue			GD 4
	Normal			GD 0-GD 3
	Normal			GD 5-GD 15
	Scheduled Sacrifice			GD 16
691	Blue Tongue			GD 6
	Normal			GD 0-GD 5
	Normal			GD 7-GD 15
	Scheduled Sacrifice			GD 16
692	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
693	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
694	Blue Tongue			GD 2
	Normal			GD 0-GD 1
	Normal			GD 3-GD 15
	Scheduled Sacrifice			GD 16
695	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
696	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16

ORAL FERTILITY AND EARLY EMBRYONIC
DEVELOPMENT STUDY OF WR6026
DIHYDROCHLORIDE IN RATS

INDIVIDUAL CLINICAL SIGNS

STUDY: 218 GROUP: 4-F SEX: FEMALE
GD 0-GD 20 DOSE: 18(mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
697	Blue Tongue			GD 1
	Normal			GD 0
	Normal			GD 2-GD 15
	Scheduled Sacrifice			GD 16
698	Blue Tongue			GD 0
	Blue Tongue			GD 2-GD 3
	Blue Tongue			GD 6
	Normal			GD 1
	Normal			GD 4-GD 5
	Normal			GD 7-GD 15
	Scheduled Sacrifice			GD 16
699	Normal			GD 0-GD 15
	Scheduled Sacrifice			GD 16
700	Blue Tongue			GD 2
	Normal			GD 0-GD 1
	Normal			GD 3-GD 15
	Scheduled Sacrifice			GD 16

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INCIDENCE OF OBSERVATIONS

STUDY: 218 SEX: FEMALE

PERIOD	DOSE: (mg base/kg/day) GROUP:	0 1-F	3 2-F	7.5 3-F	18 4-F
GD 0					
	No. Observed	22	24	23	24
	Normal	22 100%	24 100%	23 100%	23 96%
	Blue Tongue	0	0	0	1 4%
GD 1					
	No. Observed	22	24	23	24
	Normal	22 100%	24 100%	23 100%	23 96%
	Blue Tongue	0	0	0	1 4%
GD 2					
	No. Observed	22	24	23	24
	Normal	22 100%	24 100%	23 100%	20 83%
	Blue Tongue	0	0	0	4 17%
GD 3					
	No. Observed	22	24	23	24
	Normal	22 100%	24 100%	23 100%	21 88%
	Blue Tongue	0	0	0	3 12%
GD 4					
	No. Observed	22	24	23	24
	Normal	22 100%	24 100%	23 100%	22 92%
	Blue Tongue	0	0	0	2 8%
GD 5					
	No. Observed	22	24	23	24
	Normal	22 100%	24 100%	23 100%	24 100%
GD 6					
	No. Observed	22	24	23	24
	Normal	22 100%	24 100%	23 100%	21 88%
	Blue Tongue	0	0	0	3 12%
GD 7					
	No. Observed	22	24	23	24
	Normal	22 100%	24 100%	23 100%	24 100%
GD 8					
	No. Observed	22	24	23	24
	Normal	22 100%	24 100%	23 100%	24 100%

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INCIDENCE OF OBSERVATIONS

STUDY: 218 SEX: FEMALE

PERIOD	DOSE: (mg base/kg/day) / GROUP:	0 / 1-F	3 / 2-F	7.5 / 3-F	18 / 4-F
GD 9					
	No. Observed	22	24	23	24
	Normal	22 100%	24 100%	23 100%	24 100%
GD 10					
	No. Observed	22	24	23	24
	Normal	22 100%	24 100%	23 100%	24 100%
GD 11					
	No. Observed	22	24	23	24
	Normal	22 100%	24 100%	23 100%	24 100%
GD 12					
	No. Observed	22	24	23	24
	Normal	22 100%	24 100%	23 100%	24 100%
GD 13					
	No. Observed	22	24	23	24
	Normal	22 100%	24 100%	23 100%	24 100%
GD 14					
	No. Observed	22	24	23	24
	Normal	22 100%	24 100%	23 100%	24 100%
GD 15					
	No. Observed	22	24	23	24
	Normal	22 100%	24 100%	23 100%	24 100%
GD 16					
	No. Observed	22	24	23	24
	Scheduled Sacrifice	22 100%	23 96%	23 100%	24 100%
	Normal	0	1 4%	0	0
GD 17					
	No. Observed	0	1	0	0
	Scheduled Sacrifice [a]	0	1 100%	0	0
GD 18					
	No. Observed	0	0	0	0
GD 19					
	No. Observed	0	0	0	0
GD 20					
	No. Observed	0	0	0	0

[a]Animal No. 647 was inadvertently sacrificed on gestation day 17. This animals was correctly dosed throughout the precohabitation and cohabitation phases as well as from gestation days 0 - 6.

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 218 GROUP: 1-F SEX: FEMALE
DOSE: 0 (mg base/kg/day)

ANIMAL #	GD 0	GD 1	GD 2	GD 3	GD 4	GD 5	GD 6	GD 10	GD 13	GD 16
601	254	261	272	274	277	283	287	310	327	355
602	248	264	270	275	281	284	287	312	325	353
603	246	266	275	281	279	282	287	303	316	346
604	--	--	--	--	--	--	--	--	--	b
605	--	--	--	--	--	--	--	--	--	--
606	265	276	281	282	291	293	296	322	341	374
607	--	--	--	--	--	--	--	--	--	--
608	233	237	242	248	255	251	254	275	293	320
609	225	239	239	245	249	254	255	274	288	312
610	--	--	--	--	--	--	--	--	--	b
611	244	249	257	263	269	268	272	295	303	322
612	265	271	278	280	285	284	292	302	318	335
613	243	258	259	263	260	272	269	282	299	320
614	254	264	265	273	279	284	283	307	321	362
615	256	259	267	271	273	277	281	294	308	337
616	247	257	267	268	269	273	278	287	305	331
617	252	255	258	269	256	275	278	301	321	348
618	240	243	247	250	245	256	260	282	298	315
619	269	275	280	290	294	282	299	321	342	364
620	230	241	252	257	260	263	270	297	312	337
621	249	259	264	271	277	277	284	303	321	345
622	294	305	308	313	319	325	330	347	368	391
623	--	--	--	--	--	--	--	--	--	--
624	211	221	228	234	239	241	240	262	274	298
625	253	262	264	268	267	269	275	295	305	328
MEAN	249	258	264	269	271	275	279	299	314	340
S.D.	17.6	17.7	17.6	17.3	18.7	17.8	19.2	19.3	21.0	22.8
N	20	20	20	20	20	20	20	20	20	20

--: Data Unavailable b: Scheduled Sacrifice

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ORAL FERTILITY AND EARLY EMBRYONIC
DEVELOPMENT STUDY OF WR6026
DIHYDROCHLORIDE IN RATS

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 218 GROUP: 2-F SEX: FEMALE
DOSE: 3(mg base/kg/day)

ANIMAL #	GD 0	GD 1	GD 2	GD 3	GD 4	GD 5	GD 6	GD 10	GD 13	GD 16
626	236	247	255	260	263	265	269	287	302	322
627	254	266	271	275	274	279	287	303	324	358
628	259	270	270	279	281	285	285	302	328	349
629	--	--	--	--	--	--	--	--	--	--
630	253	262	263	274	274	279	282	304	323	349
631	242	249	253	258	262	261	265	280	299	315
632	241	254	260	256	260	269	266	281	293	317
633	247	265	266	269	271	274	280	303	313	340
634	239	243	251	254	258	261	267	286	302	332
635	237	242	250	253	260	259	262	275	307	334
636	235	239	248	250	254	260	264	283	303	327
637	216	227	235	237	245	251	255	277	297	322
638	253	265	272	279	280	287	283	304	320	345
639	266	276	278	285	289	292	292	314	334	369
640	250	267	270	271	283	284	286	309	331	352
641	267	274	289	289	297	293	293	317	329	359
642	242	250	248	253	257	264	263	279	302	320
643	264	273	277	284	296	298	300	329	348	374
644	230	241	244	247	249	251	256	278	295	317
645	270	278	282	287	289	293	297	313	326	354
646	249	256	258	257	256	261	268	289	305	325
647	239	252	258	256	261	262	263	278	299	--
648	302	310	315	319	329	328	330	352	377	388
649	248	254	257	261	267	270	268	289	299	325
650	254	258	263	267	267	270	275	294	308	338
MEAN	250	259	264	268	272	275	277	297	315	340
S.D.	16.9	17.1	16.9	17.8	18.9	17.9	17.2	19.1	19.8	20.2
N	24	24	24	24	24	24	24	24	24	23

--: Data Unavailable

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INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 218 GROUP: 3-F SEX: FEMALE
DOSE: 7.5 (mg base/kg/day)

ANIMAL #	GD 0	GD 1	GD 2	GD 3	GD 4	GD 5	GD 6	GD 10	GD 13	GD 16
651	228	238	242	244	250	254	255	278	293	322
652	254	258	262	269	274	274	278	299	318	351
653	243	246	252	256	261	269	264	285	309	328
654	243	257	255	256	263	262	259	279	294	324
655	221	231	235	236	239	245	246	266	287	314
656	278	283	289	294	298	302	302	324	350	374
657	232	238	238	243	244	246	245	263	271	288
658	221	228	229	232	236	243	244	267	289	318
659	278	283	287	289	286	293	295	318	339	361
661	221	232	244	244	246	250	253	275	291	302
662	254	267	269	271	274	273	278	303	312	326
663	238	248	257	260	262	264	270	301	306	334
664	222	241	244	246	247	247	248	267	282	303
665	230	239	248	244	251	253	260	277	292	310
666	249	261	270	274	275	276	280	297	318	342
667	248	254	264	266	264	266	276	300	318	352
668	276	285	287	290	294	299	305	324	344	359
669	224	240	248	255	259	263	264	288	298	316
670	255	258	267	272	273	274	283	314	328	352
671	--	--	--	--	--	--	--	--	--	b
672	226	236	244	250	247	248	252	275	291	318
673	248	260	265	265	273	270	272	294	308	327
674	--	--	--	--	--	--	--	--	--	--
675	243	261	264	269	273	274	281	303	324	345
MEAN	242	252	257	260	263	266	269	291	307	330
S.D.	18.4	17.1	16.9	17.4	17.2	17.1	18.1	19.1	20.9	21.9
N	22	22	22	22	22	22	22	22	22	22

--: Data Unavailable b: Scheduled Sacrifice

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 218 GROUP: 4-F SEX: FEMALE
DOSE: 18(mg base/kg/day)

ANIMAL #	GD 0	GD 1	GD 2	GD 3	GD 4	GD 5	GD 6	GD 10	GD 13	GD 16
676	247	264	264	270	274	278	275	300	325	349
677	217	227	228	227	234	235	238	255	275	299
678	247	250	258	258	264	268	271	292	309	349
679	222	226	230	232	238	237	238	260	283	310
680	221	228	233	236	240	242	244	268	286	307
681	215	226	232	231	237	242	239	259	278	298
682	--	--	--	--	--	--	--	--	--	b
683	256	266	274	273	277	276	287	312	336	366
684	213	226	232	240	246	250	250	269	286	314
685	249	257	262	265	268	271	276	299	310	338
686	254	257	267	269	273	279	283	299	316	333
687	238	255	259	257	259	256	257	292	317	348
688	--	--	--	--	--	--	--	--	--	--
689	--	--	--	--	--	--	--	--	--	b
690	237	246	253	252	253	258	261	280	302	321
691	239	237	252	258	262	271	272	292	311	346
692	252	264	268	268	266	270	274	292	321	347
693	219	229	235	231	237	241	246	257	282	308
694	277	291	292	294	297	301	305	335	355	386
695	225	229	237	240	243	246	249	269	292	308
696	223	235	238	237	244	247	246	261	274	297
697	210	217	222	222	230	228	232	250	261	291
698	240	240	248	252	252	256	266	276	294	319
699	247	261	267	269	274	278	278	302	322	347
700	245	257	250	252	260	259	267	288	304	321
MEAN	236	245	250	252	256	259	262	282	302	327
S.D.	17.3	18.6	18.1	18.5	17.4	18.3	19.1	21.7	23.0	25.1
N	22	22	22	22	22	22	22	22	22	22

--: Data Unavailable b: Scheduled Sacrifice

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 218 GROUP: 1-F SEX: FEMALE
DOSE: 0(mg base/kg/day)

ANIMAL #	GD 1[c]	GD 2	GD 3	GD 4	GD 5	GD 6	GD 10	GD 13	GD 16	TOTAL GAIN
601	7	11	2	3	6	4	23	17	28	101
602	16	6	5	6	3	3	25	13	28	105
603	20	9	6	-2	3	5	16	13	30	100
604	--	--	--	--	--	--	--	--	b	--
605	--	--	--	--	--	--	--	--	--	--
606	11	5	1	9	2	3	26	19	33	109
607	--	--	--	--	--	--	--	--	--	--
608	4	5	6	7	-4	3	21	18	27	87
609	14	0	6	4	5	1	19	14	24	87
610	--	--	--	--	--	--	--	--	b	--
611	5	8	6	6	-1	4	23	8	19	78
612	6	7	2	5	-1	8	10	16	17	70
613	15	1	4	-3	12	-3	13	17	21	77
614	10	1	8	6	5	-1	24	14	41	108
615	3	8	4	2	4	4	13	14	29	81
616	10	10	1	1	4	5	9	18	26	84
617	3	3	11	-13	19	3	23	20	27	96
618	3	4	3	-5	11	4	22	16	17	75
619	6	5	10	4	-12	17	22	21	22	95
620	11	11	5	3	3	7	27	15	25	107
621	10	5	7	6	0	7	19	18	24	96
622	11	3	5	6	6	5	17	21	23	97
623	--	--	--	--	--	--	--	--	--	--
624	10	7	6	5	2	-1	22	12	24	87
625	9	2	4	-1	2	6	20	10	23	75
MEAN	9	6	5	2	3	4	20	16	25	91
S.D.	4.7	3.3	2.7	5.1	6.3	4.1	5.2	3.5	5.5	12.3
N	20	20	20	20	20	20	20	20	20	20

--: Data Unavailable b: Scheduled Sacrifice

[a]Weight gains compared to the previous period
[c]Baseline is gestation day 0

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 218 GROUP: 2-F SEX: FEMALE
DOSE: 3 (mg base/kg/day)

ANIMAL #	GD 1[c]	GD 2	GD 3	GD 4	GD 5	GD 6	GD 10	GD 13	GD 16	TOTAL GAIN
626	11	8	5	3	2	4	18	15	20	86
627	12	5	4	-1	5	8	16	21	34	104
628	11	0	9	2	4	0	17	26	21	90
629	--	--	--	--	--	--	--	--	--	--
630	9	1	11	0	5	3	22	19	26	96
631	7	4	5	4	-1	4	15	19	16	73
632	13	6	-4	4	9	-3	15	12	24	76
633	18	1	3	2	3	6	23	10	27	93
634	4	8	3	4	3	6	19	16	30	93
635	5	8	3	7	-1	3	13	32	27	97
636	4	9	2	4	6	4	19	20	24	92
637	11	8	2	8	6	4	22	20	25	106
638	12	7	7	1	7	-4	21	16	25	92
639	10	2	7	4	3	0	22	20	35	103
640	17	3	1	12	1	2	23	22	21	102
641	7	15	0	8	-4	0	24	12	30	92
642	8	-2	5	4	7	-1	16	23	18	78
643	9	4	7	12	2	2	29	19	26	110
644	11	3	3	2	2	5	22	17	22	87
645	8	4	5	2	4	4	16	13	28	84
646	7	2	-1	-1	5	7	21	16	20	76
647	13	6	-2	5	1	1	15	21	--	60
648	8	5	4	10	-1	2	22	25	11	86
649	6	3	4	6	3	-2	21	10	26	77
650	4	5	4	0	3	5	19	14	30	84
MEAN	9	5	4	4	3	3	20	18	25	89
S.D.	3.8	3.6	3.4	3.7	3.0	3.1	3.7	5.3	5.6	11.9
N	24	24	24	24	24	24	24	24	23	24

--: Data Unavailable b: Scheduled Sacrifice

[a]Weight gains compared to the previous period
[c]Baseline is gestation day 0

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 218 GROUP: 3-F SEX: FEMALE
DOSE: 7.5(mg base/kg/day)

ANIMAL #	GD 1[c]	GD 2	GD 3	GD 4	GD 5	GD 6	GD 10	GD 13	GD 16	TOTAL GAIN
651	10	4	2	6	4	1	23	15	29	94
652	4	4	7	5	0	4	21	19	33	97
653	3	6	4	5	8	-5	21	24	19	85
654	14	-2	1	7	-1	-3	20	15	30	81
655	10	4	1	3	6	1	20	21	27	93
656	5	6	5	4	4	0	22	26	24	96
657	6	0	5	1	2	-1	18	8	17	56
658	7	1	3	4	7	1	23	22	29	97
659	5	4	2	-3	7	2	23	21	22	83
661	11	12	0	2	4	3	22	16	11	81
662	13	2	2	3	-1	5	25	9	14	72
663	10	9	3	2	2	6	31	5	28	96
664	19	3	2	1	0	1	19	15	21	81
665	9	9	-4	7	2	7	17	15	18	80
666	12	9	4	1	1	4	17	21	24	93
667	6	10	2	-2	2	10	24	18	34	104
668	9	2	3	4	5	6	19	20	15	83
669	16	8	7	4	4	1	24	10	18	92
670	3	9	5	1	1	9	31	14	24	97
671	--	--	--	--	--	--	--	--	b	--
672	10	8	6	-3	1	4	23	16	27	92
673	12	5	0	8	-3	2	22	14	19	79
674	--	--	--	--	--	--	--	--	--	--
675	18	3	5	4	1	7	22	21	21	102
MEAN	10	5	3	3	3	3	22	17	23	88
S.D.	4.6	3.6	2.6	3.0	2.9	3.7	3.6	5.4	6.2	11.1
N	22	22	22	22	22	22	22	22	22	22

--: Data Unavailable b: Scheduled Sacrifice

[a]Weight gains compared to the previous period
[c]Baseline is gestation day 0

DRAFT

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 218 GROUP: 4-F SEX: FEMALE
DOSE: 18 (mg base/kg/day)

ANIMAL #	GD 1[c]	GD 2	GD 3	GD 4	GD 5	GD 6	GD 10	GD 13	GD 16	TOTAL GAIN
676	17	0	6	4	4	-3	25	25	24	102
677	10	1	-1	7	1	3	17	20	24	82
678	3	8	0	6	4	3	21	17	40	102
679	4	4	2	6	-1	1	22	23	27	88
680	7	5	3	4	2	2	24	18	21	86
681	11	6	-1	6	5	-3	20	19	20	83
682	--	--	--	--	--	--	--	--	b	--
683	10	8	-1	4	-1	11	25	24	30	110
684	13	6	8	6	4	0	19	17	28	101
685	8	5	3	3	3	5	23	11	28	89
686	3	10	2	4	6	4	16	17	17	79
687	17	4	-2	2	-3	1	35	25	31	110
688	--	--	--	--	--	--	--	--	--	--
689	--	--	--	--	--	--	--	--	b	--
690	9	7	-1	1	5	3	19	22	19	84
691	-2	15	6	4	9	1	20	19	35	107
692	12	4	0	-2	4	4	18	29	26	95
693	10	6	-4	6	4	5	11	25	26	89
694	14	1	2	3	4	4	30	20	31	109
695	4	8	3	3	3	3	20	23	16	83
696	12	3	-1	7	3	-1	15	13	23	74
697	7	5	0	8	-2	4	18	11	30	81
698	0	8	4	0	4	10	10	18	25	79
699	14	6	2	5	4	0	24	20	25	100
700	12	-7	2	8	-1	8	21	16	17	76
MEAN	9	5	1	4	3	3	21	20	26	91
S.D.	5.2	4.2	2.9	2.6	2.9	3.6	5.6	4.7	6.0	11.8
N	22	22	22	22	22	22	22	22	22	22

--: Data Unavailable b: Scheduled Sacrifice

[a]Weight gains compared to the previous period
[c]Baseline is gestation day 0

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 218 GROUP: 1-F SEX: FEMALE
DOSE: 0 (mg base/kg/day)

ANIMAL #	GD 3[b]	GD 6	GD 10	GD 13	GD 16
601	20.0	21.7	22.3	28.7	21.7
602	22.3	23.0	24.3	22.7	26.3
603	22.7	21.7	22.5	22.0	25.3
604	--	--	--	--	--
605	--	--	--	--	--
606	23.7	23.7	27.0	26.7	31.0
607	--	--	--	--	--
608	18.7	18.0	19.0	21.0	22.3
609	19.3	20.7	20.0	21.7	23.3
610	--	--	--	--	--
611	24.0	23.0	24.3	23.0	25.0
612	20.0	21.3	19.0	22.7	20.3
613	18.7	18.0	19.8	22.0	20.3
614	21.0	22.0	23.5	24.0	27.7
615	19.7	20.7	20.0	22.0	25.3
616	19.0	21.7	20.3	23.7	19.0
617	20.3	21.3	23.0	24.7	26.0
618	17.7	22.3	23.8	25.0	23.3
619	22.0	22.3	25.8	25.0	25.7
620	21.3	21.7	24.0	24.0	27.7
621	23.0	23.0	23.5	23.0	26.0
622	23.7	24.3	24.5	25.7	25.0
623	--	--	--	--	--
624	20.0	20.3	21.0	22.0	22.0
625	19.0	19.3	21.3	21.0	22.7
MEAN	20.8	21.5	22.4	23.5	24.3
S.D.	1.92	1.67	2.30	1.99	2.93
N	20	20	20	20	20

--: Data Unavailable

[a]Calculated daily food consumption for successive period intervals
[b]Baseline is gestation day 0

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 218 GROUP: 2-F SEX: FEMALE
DOSE: 3 (mg base/kg/day)

ANIMAL #	GD 3[b]	GD 6	GD 10	GD 13	GD 16
626	19.3	18.7	21.5	23.7	24.3
627	20.3	20.0	22.0	24.0	26.0
628	21.7	21.7	23.0	27.7	26.0
629	--	--	--	--	--
630	21.0	19.3	24.5	24.7	26.3
631	20.0	22.3	19.8	26.0	24.7
632	19.3	19.3	21.0	20.7	24.0
633	20.0	21.3	23.8	21.3	25.0
634	20.0	21.7	25.3	31.7	14.7
635	17.7	20.7	25.3	19.3	26.7
636	17.7	21.3	26.3	7.3	27.3
637	17.3	20.3	22.3	24.0	22.7
638	20.7	19.7	22.5	23.0	23.7
639	19.7	19.3	22.5	27.7	28.3
640	20.7	23.3	24.5	25.3	24.0
641	21.0	19.0	24.0	26.3	25.7
642	20.3	20.3	22.0	23.3	22.3
643	20.3	22.0	24.8	28.0	26.7
644	16.7	17.7	18.0	23.0	22.0
645	20.7	22.7	20.8	20.7	27.0
646	19.0	20.3	23.8	25.7	25.3
647	17.7	18.3	21.3	22.0	--
648	23.3	25.3	26.8	32.0	26.3
649	18.7	53.7	--	22.0	22.0
650	18.3	20.3	21.5	22.0	22.3
MEAN	19.6	22.0	22.9	23.8	24.5
S.D.	1.55	6.96	2.13	4.78	2.81
N	24	24	23	24	23

--: Data Unavailable

[a]Calculated daily food consumption for successive period intervals
[b]Baseline is gestation day 0

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 218 GROUP: 3-F SEX: FEMALE
DOSE: 7.5 (mg base/kg/day)

ANIMAL #	GD 3[b]	GD 6	GD 10	GD 13	GD 16
651	18.3	17.3	20.0	21.0	21.3
652	19.7	21.3	23.0	23.3	28.3
653	19.7	18.7	21.3	24.0	21.0
654	18.3	17.0	19.3	25.0	24.0
655	17.7	17.3	20.3	20.7	24.3
656	20.3	21.0	23.0	26.3	26.7
657	16.7	16.3	18.3	19.0	19.0
658	16.7	16.3	19.8	22.7	24.3
659	18.7	17.7	22.3	29.0	24.7
661	18.0	17.3	21.3	23.3	21.7
662	18.7	18.3	21.3	22.0	23.0
663	19.0	20.3	22.3	21.3	22.3
664	18.3	15.0	17.8	21.0	18.0
665	18.7	20.7	21.3	21.7	18.0
666	19.7	19.0	23.3	24.0	24.7
667	17.7	19.7	23.5	24.7	25.7
668	22.3	23.7	26.5	24.7	25.3
669	21.0	19.7	23.5	22.7	22.3
670	21.0	20.3	24.8	27.0	27.3
671	--	--	--	--	--
672	17.3	15.7	20.0	24.0	25.7
673	18.3	19.0	21.0	22.0	21.3
674	--	--	--	--	--
675	19.7	20.3	21.8	22.7	19.7
MEAN	18.9	18.7	21.6	23.3	23.1
S.D.	1.42	2.13	2.08	2.29	2.92
N	22	22	22	22	22

--: Data Unavailable

[a]Calculated daily food consumption for successive period intervals
[b]Baseline is gestation day 0

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

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INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 218 GROUP: 4-F SEX: FEMALE
DOSE: 18 (mg base/kg/day)

ANIMAL #	GD 3[b]	GD 6	GD 10	GD 13	GD 16
676	20.0	19.0	24.8	27.7	26.3
677	15.0	17.3	18.8	23.0	24.3
678	15.3	17.3	21.0	24.7	29.3
679	15.7	16.7	20.3	24.3	26.3
680	16.7	17.7	20.0	23.0	24.0
681	24.3	12.7	19.3	23.0	21.7
682	--	--	--	--	--
683	19.0	20.0	25.0	29.0	27.3
684	16.7	17.3	20.3	23.3	23.7
685	19.0	20.0	22.5	24.7	19.7
686	17.0	19.0	22.5	22.3	19.3
687	17.7	14.3	22.0	27.7	26.3
688	--	--	--	--	--
689	--	--	--	--	--
690	16.0	16.3	17.8	9.3	34.0
691	16.3	18.3	20.3	27.3	27.7
692	17.0	16.3	21.5	27.7	29.0
693	13.3	18.3	13.3	26.0	19.3
694	20.3	23.0	25.8	27.3	28.3
695	16.7	19.7	21.3	24.7	24.7
696	14.7	14.0	14.5	21.7	22.3
697	14.7	13.7	17.0	18.0	18.7
698	14.7	17.3	17.5	20.3	24.0
699	19.7	19.7	22.3	26.0	25.0
700	15.0	18.0	20.0	20.0	21.3
MEAN	17.0	17.5	20.4	23.7	24.7
S.D.	2.52	2.41	3.11	4.30	3.84
N	22	22	22	22	22

--: Data Unavailable

[a]Calculated daily food consumption for successive period intervals
[b]Baseline is gestation day 0

APPENDIX F

INDIVIDUAL FEMALE REPRODUCTIVE DATA

- Individual Cesarean Section Data
- Individual Estrus Data

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

Individual Maternal Cesarean Section Data

Dose Level (mg base/kg/day)	Dam No.	Total Implantations	Corpora Lutea	Resorptions		Viable Fetuses per Dam	Nonviable Fetuses per Dam	Gross Dam Observations
				Early	Late			
0	601	15	15	0	0	15	0	Normal
	607	17	17	0	0	17	0	Normal
	603	16	16	0	0	16	0	Normal
	605	15	16	a	a	a	a	Normal
	606	18	23	2	0	16	0	Normal
	607	17	18	2	a	a	a	Normal
	603	16	16	0	0	16	0	Normal
	609	14	16	0	0	14	0	Normal
	611	13	13	0	0	13	0	Normal
	622	15	17	2	0	13	0	Normal
	622	18	18	0	0	18	0	Normal
	614	17	17	0	0	17	0	Normal
	622	16	16	2	0	14	0	Normal
	616	15	16	0	0	15	0	Normal
	622	15	15	2	0	13	0	Normal
	622	13	13	2	0	12	0	Normal
	622	18	18	0	0	18	0	Normal
	620	15	15	0	0	15	0	Normal
	622	19	19	3	0	16	0	Normal
	622	15	16	0	0	15	0	Normal
	622	15	15	2	0	14	0	Normal
	625	14	14	1	0	13	0	Normal

a = Animal Sperm-Negative, Palpated Pregnant
Animal Nos. 604 and 610 were Sperm-Positive, Non-Gravid
Animal No. 623 was Sperm-Negative, Non-Gravid

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

Individual Maternal Cesarean Section Data

Dose Level (mg base/kg/day)	Dam No.	Preimplantation Loss %	Postimplantation Loss %	Total Implantation Loss %
0	601	0	0	0
	602	0	0	0
	603	0	0	0
	605	6	a	a
	606	22	11	30
	607	6	a	a
	608	0	0	0
	609	13	0	13
	611	0	0	0
	612	12	13	24
	613	0	0	0
	614	0	0	0
	615	0	13	13
	616	6	0	6
	617	0	13	13
	618	0	8	8
	619	0	0	0
	620	0	0	0
	621	0	16	16
	622	6	0	6
	624	0	7	7
	625	0	7	7

a = Animal Sperm-Negative, Palpated Pregnant
Animal Nos. 604 and 610 were Sperm-Positive, Non-Gravid
Animal No. 623 was Sperm-Negative, Non-Gravid

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

Individual Maternal Cesarean Section Data

Dose Level (mg base/kg/day)	Dam No.	Total Implantations	Corpora Lutea	Resorptions		Viable Fetuses per Dam	Nonviable Fetuses per Dam	Gross Dam Observations
				Early	Late			
3.0	626	15	15	3	0	12	0	Normal
	627	16	16	0	0	16	0	Normal
	628	16	16	0	0	15	1	Normal
	630	17	19	1	0	16	0	Normal
	631	13	13	0	0	13	0	Normal
	632	16	16	0	0	16	0	Normal
	633	15	17	0	0	15	0	Normal
	634	14	16	1	0	13	0	Normal
	635	17	17	1	0	16	0	Mottled Kidneys
	636	13	14	1	0	12	0	Normal
	637	17	18	2	0	15	0	Normal
	638	15	15	2	0	13	0	Normal
	639	17	17	2	0	15	0	Normal
	640	17	18	1	0	16	0	Normal
	641	16	16	1	0	15	0	Normal
	642	15	15	0	0	15	0	Normal
	643	14	14	0	0	14	0	Normal
	644	16	21	0	0	16	0	Normal
	645	17	19	1	0	16	0	Normal
	646	12	13	1	0	14	0	Normal
	647	14	14	0	0	14	0	Normal
	648	18	25	2	0	16	0	Normal
	649	14	14	1	0	13	0	Normal
	650	16	16	0	0	16	0	Mottled Kidneys

a = Animal Sperm-Negative, Palpated Pregnant
Animal Nos. 604 and 610 were Sperm-Positive, Non-Gravid
Animal No. 623 was Sperm-Negative, Non-Gravid

ORAL FERTILITY AND EARLY EMBRYONIC
DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

Individual Maternal Cesarean Section Data

Dose Level (mg base/kg/day)	Dam No.	Preimplantation Loss %	Postimplantation Loss %	Total Implantation Loss %
3.0	626	0	20	20
	627	0	0	0
	628	0	6	6
	630	11	6	16
	631	0	0	0
	632	0	0	0
	633	12	0	12
	634	13	7	19
	635	0	6	6
	636	7	8	14
	637	6	12	17
	638	0	13	13
	639	0	12	12
	640	6	6	11
	641	0	6	6
	642	0	0	0
	643	0	0	0
	645	24	0	24
	647	11	6	16
	646	8	8	15
	631	0	0	0
	648	28	11	36
	649	0	7	7
	650	0	0	0

a = Animal Sperm-Negative, Palpated Pregnant
Animal Nos. 604 and 610 were Sperm-Positive, Non-Gravid
Animal No. 623 was Sperm-Negative, Non-Gravid

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

Individual Maternal Cesarean Section Data

Dose Level (mg base/kg/day)	Dam No.	Total Implantations	Corpora Lutea	Resorptions		Viable Fetuses per Dam	Nonviable Fetuses per Dam	Gross Dam Observations
				Early	Late			
7.5	651	14	16	1	0	13	0	Normal
	667	17	19	0	0	17	0	Normal
	653	14	14	0	0	14	0	Normal
	654	16	16	1	0	15	0	Normal
	655	14	14	7	0	13	0	Normal
	656	14	16	1	0	13	0	Normal
	657	14	14	6	0	8	0	Normal
	658	16	21	0	0	16	0	Normal
	659	13	14	1	0	12	0	Normal
	661	13	13	7	0	6	0	Normal
	662	5	15	0	0	5	0	Normal
	663	16	16	7	0	14	0	Normal
	664	14	14	1	0	13	0	Normal
	665	15	15	0	0	15	0	Normal
	666	15	15	0	0	15	0	Normal
	667	15	15	0	0	15	0	Normal
	668	14	23	0	0	14	0	Normal
	669	14	15	3	0	11	0	Normal
	670	17	17	1	0	16	0	Normal
	672	12	14	0	0	12	0	Normal
	673	14	14	3	0	13	0	Normal
	674	19	23	a	a	a	a	Normal
	675	15	16	0	0	15	0	Normal

a = Animal Sperm-Negative, Palpated Pregnant
Animal No. 660 Died on Precohabitation Day 13
Animal No. 671 was Sperm Positive, Non-Gravid

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

Individual Maternal Cesarean Section Data

Dose Level (mg base/kg/day)	Dam No.	Preimplantation Loss %	Postimplantation Loss %	Total Implantation Loss %
7.5	651	13	7	19
	652	11	0	11
	653	0	0	0
	654	0	6	6
	655	0	7	7
	656	13	7	19
	657	0	43	43
	658	24	0	24
	659	7	8	14
	661	0	54	54
	662	67	0	67
	663	0	13	13
	664	0	7	7
	665	0	0	0
	666	0	0	0
	667	0	0	0
	668	39	0	39
	669	7	21	27
	670	0	6	6
	672	14	0	14
	673	0	7	7
	674	17	a	a
	675	6	0	6

a = Animal Sperm-Negative, Palpated Pregnant
Animal No. 660 Died on Precohabitation Day 13
Animal No. 671 was Sperm Positive, Non-Gravid

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

Individual Maternal Cesarean Section Data

Dose Level (mg base/kg/day)	Dam No.	Total Implantations	Corpora Lutea	Resorptions		Viable Fetuses per Dam	Nonviable Fetuses per Dam	Gross Dam Observations
				Early	Late			
18.0	676	15	16	1	0	14	0	Normal
	681	13	13	0	0	13	0	Normal
	679	13	14	0	0	13	0	Normal
	679	12	13	1	0	11	0	Normal
	680	12	13	2	0	111	0	Normal
	681	13	13	0	0	13	0	Normal
	683	16	17	0	0	16	0	Normal
	684	14	16	0	0	14	0	Normal
	681	15	15	1	0	14	0	Normal
	686	14	15	1	0	13	0	Normal
	687	14	15	0	0	14	0	Normal
	693	16	18	1	a	a	a	Normal
	690	12	13	1	0	11	0	Normal
	691	15	18	2	0	13	0	Normal
	687	14	14	0	0	14	0	Normal
	693	13	16	0	0	13	0	Normal
	693	16	16	1	0	15	0	Normal
	695	16	16	1	0	14	0	Normal
	696	10	10	0	0	10	0	Normal
	693	14	14	0	0	14	0	Normal
	698	15	15	0	0	15	0	Normal
	693	15	15	1	0	0	0	Normal
	700	13	14	0	0	13	0	Normal

a = Animal Sperm-Negative, Palpated Pregnant
Animal Nos. 682 and 689 were Sperm Positive, Non-Gravid

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

Individual Maternal Cesarean Section Data

Dose Level (mg base/kg/day)	Dam No.	Preimplantation Loss %	Postimplantation Loss %	Total Implantation Loss %
18.0	676	6	7	13
	698	0	0	0
	678	7	0	7
	679	8	8	15
	680	8	17	23
	681	0	0	0
	683	6	0	6
	684	13	0	13
	685	0	7	7
	686	7	7	13
	687	7	0	7
	688	11	a	a
	690	8	8	15
	691	17	13	28
	694	0	0	0
	695	19	0	19
	694	0	6	6
	695	0	13	13
	695	0	0	0
	697	0	0	0
	698	0	0	0
	699	0	7	7
	700	7	0	7

a = Animal Sperm-Negative, Palpated Pregnant
Animal Nos. 682 and 689 were Sperm Positive, Non-Gravid

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

Individual Estrus Cycle Data

		Precohabitation Estrus Cycle Data				
Dose Level (mg base/kg/day)	Dam No.	No. Occurrences of Estrus	No. Days in Interval	Average Cycle Length	Mating Male No.	No. of Days of Cohabitation
0	601	3	9	4.50	501	1
	602	4	12	4.00	502	2
	603	3	8	4.00	503	1
	603	4	12	4.00	504	c
	605	3	10	5.00	505	b
	606	3	8	4.00	506	1
	607	4	12	4.00	507	b
	608	4	12	4.00	508	2
	609	3	11	5.50	509	1
	610	4	12	4.00	510	c
	611	4	12	4.00	511	2
	612	4	12	4.00	512	3
	616	4	14	4.67	513	1
	616	3	8	4.00	514	1
	616	a	a	a	515	3
	616	3	10	4.00	516	4
	617	a	a	a	517	3
	616	5	12	4.00	518	3
	619	4	12	4.00	519	2
	620	3	8	4.00	520	1
	621	4	12	4.00	521	2
	621	4	12	4.00	522	4
	621	d	d	d	523	d
	616	a	a	a	524	1
	625	4	12	4.00	525	3

a = Animal Excluded Due to Insufficient Number of Cycles
b = Animal Sperm Negative, Palpated, Pregnant; Gestation Day 0 Unknown
c = Animal Sperm Positive, Non-Gravid
d = Animal Sperm Negative, Non-Gravid
e = Animal Not Cohabitated, Died on Precohabitation Day 13; Male No. 560 not mated

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

Individual Estrus Cycle Data

		Precohabitation Estrus Cycle Data				
Dose Level (mg base/kg/day)	Dam No.	No. Occurrences of Estrus	No. Days in Interval	Average Cycle Length	Mating Male No.	No. of Days of Cohabitation
3.0	626	4	14	4.67	526	1
	629	4	12	4.00	527	3
	628	3	9	4.50	528	3
	629	d	d	d	529	d
	630	3	8	4.00	530	1
	631	4	12	4.00	531	2
	632	3	8	4.00	532	1
	633	3	8	4.00	533	1
	635	4	12	4.00	534	4
	635	4	12	4.00	535	2
	636	4	12	4.00	536	2
	637	a	a	a	537	5
	638	a	a	d	538	1
	639	3	8	4.00	539	1
	640	4	12	4.00	540	2
	643	3	8	4.00	541	1
	642	3	10	5.00	542	4
	643	3	8	4.00	543	1
	644	3	10	4.00	544	3
	643	3	10	4.00	545	3
	643	4	12	4.00	546	3
	643	4	14	4.67	547	1
	643	4	14	4.67	548	4
	643	3	10	5.00	549	1
	650	4	12	4.00	550	3

a = Animal Excluded Due to Insufficient Number of Cycles
b = Animal Sperm Negative, Palpated, Pregnant; Gestation Day 0 Unknown
c = Animal Sperm Positive, Non-Gravid
d = Animal Sperm Negative, Non-Gravid
e = Animal Not Cohabitated, Died on Precohabitation Day 13; Male No. 560 not mated

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

Individual Estrus Cycle Data

		Precohabitation Estrus Cycle Data				
Dose Level (mg base/kg/day)	Dam No.	No. Occurrences of Estrus	No. Days in Interval	Average Cycle Length	Mating Male No.	No. of Days of Cohabitation
7.5	651	4	13	4.33	551	1
	652	5	12	3.00	552	1
	653	4	12	4.00	553	1
	666	3	8	4.00	554	1
	655	4	12	4.00	555	3
	666	3	8	4.00	554	1
	657	4	12	4.00	557	1
	658	4	12	4.00	554	1
	659	3	8	4.00	559	1
	660	e	e	e	560	1
	661	4	12	4.00	561	1
	662	3	8	4.00	562	2
	663	3	8	4.00	563	1
	664	3	8	4.00	564	1
	666	4	12	4.00	565	1
	666	3	10	4.00	568	1
	667	4	12	4.00	567	3
	668	4	12	4.00	568	1
	669	4	13	4.33	569	1
	670	4	12	4.00	570	1
	673	4	12	4.00	571	1
	672	3	11	5.50	572	1
	673	3	8	4.00	573	1
	674	3	10	5.00	574	b
	675	3	12	6.00	575	3

a = Animal Excluded Due to Insufficient Number of Cycles
b = Animal Sperm Negative, Palpated, Pregnant; Gestation Day 0 Unknown
c = Animal Sperm Positive, Non-Gravid
d = Animal Sperm Negative, Non-Gravid
e = Animal Not Cohabitated, Died on Precohabitation Day 13; Male No. 560 not mated

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

Individual Estrus Cycle Data

		Precohabitation Estrus Cycle Data				
Dose Level (mg base/kg/day)	Dam No.	No. Occurrences of Estrus	No. Days In Interval	Average Cycle Length	Mating Male No.	No. of Days of Cohabitation
18.0	676	3	8	4.00	576	1
	677	3	10	5.00	577	2
	678	4	11	3.67	578	1
	679	4	12	4.00	579	2
	680	3	8	4.00	580	2
	681	3	9	4.50	581	1
	682	4	12	4.00	582	2
	683	4	11	3.67	583	1
	684	4	11	3.67	584	1
	685	4	13	4.33	585	3
	686	3	10	5.00	586	4
	687	3	8	4.00	587	1
	688	3	10	4.00	588	b
	689	4	12	4.00	589	1
	690	4	12	4.00	590	3
	691	3	8	4.00	591	1
	692	3	10	5.00	592	4
	693	4	7	2.33	593	1
	694	4	12	4.00	594	2
	695	4	12	4.00	595	2
	696	a	a	a	596	1
	697	4	11	3.67	597	1
	698	4	13	4.33	598	4
	699	a	a	a	599	1
	700	4	12	4.00	600	2

a = Animal Excluded Due to Insufficient Number of Cycles
b = Animal Sperm Negative, Palpated, Pregnant; Gestation Day 0 Unknown
c = Animal Sperm Positive, Non-Gravid
d = Animal Sperm Negative, Non-Gravid
e = Animal Not Cohabitated, Died on Precohabitation Day 13; Male No. 560 not mated

APPENDIX G

PROTOCOL AND AMENDMENTS

DRAFT

Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-24
Study No.: 218

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

1.0 PURPOSE OF THE STUDY:

The purpose of this study is to determine and evaluate the toxic potential of the test article on the reproductive capability of male and female rats. WR6026 Dihydrochloride is being developed as an antileishmanial agent. The scope of the study will encompass gonadal function, estrous cycles, mating, conception, implantation and early embryonic development. The experimental design of the study will involve administration of the test article to both sexes. In males, evaluation will include reproductive organ weights and sperm assessment (counts and motility). The protocol conforms with the FDA *Guideline on Detection of Toxicity to Reproduction for Medicinal Products* (1994), which was prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The protocol for this study was approved by the UIC Animal Care Committee (Appendix 1).

2.0 SPONSOR:

2.1	Name:	U.S. Army Medical Materiel Development Activity
2.2	Address:	Fort Detrick Frederick, MD 21702-5009
2.3	Representative:	George J. Schieferstein, Ph.D.

3.0 TESTING FACILITY:

3.1	Name:	Toxicology Research Laboratory (TRL)
3.2	Address:	University of Illinois at Chicago (UIC) Department of Pharmacology 1940 W. Taylor St. Chicago, IL 60612-7353
3.3	Study Director:	Debra L. Kirchner, Ph.D., D.A.B.T.

4.0 DATES:

4.1 Proposed Initiation of Dosing Phase (Males):	07/12/96
4.2 Proposed Completion of In-Life Phase:	09/24/96
4.3 Proposed Study Completion Date (Draft Final Report):	12/24/96

REVISED PAGE
STUDY NO: 218 INITIAL: dlk
DATE: 6/11/96

5.0 TEST ARTICLE

5.1 Name or Code No: WR6026 Dihydrochloride (base mole fraction = 0.825) 6-Methoxy-8-(6-diethylaminohexylamino) lepidine Dihydrochloride
Bottle No. BK01845

5.2 TRL Chemical No: 1540614

5.3 Physical Description: Light Yellow powder

5.4 Storage Conditions to Maintain Stability:

5.4.1 Temperature: -16 to -20°C during storage. 2 - 8°C following dosage formulation preparation.

5.4.2 Humidity: Hygroscopic; keep tightly closed in a desiccator

5.4.3 Light: Protect from light; amber bottle or silver foil covering.

5.4.4 Special Requirements: None.

5.5 Special Handling Procedures: Standard safety precautions will be followed including gloves, eye protection, mask. and lab coats.

5.6 Log of Test Article: The amount. date, identity of person(s) removing aliquots and the purpose for which each aliquot of the test article was removed from the batch will be documented. At termination of the study, unused test article may be returned to the Sponsor.

6.0 PERSONNEL:

Principal Investigator	Barry S. Levine, D.Sc., D.A.B.T.
Study Director	Debra L. Kirchner, Ph.D., D.A.B.T.
Sperm Assessment (PAI)	Michael D. Mercieca, B.S.
Clinical Veterinarian	James Artwohl, D.V.M., M.S., D.A.C.L.A.M.
Tox. Lab Supervisor	Soudabeh Soura, B.S.
Lead Technician	Nancy Dinger, B.S.
Chemistry Specialist	Thomas Tolhurst, B.S.
Quality Assurance	Ronald C. Schoenbeck

7.0 TEST SYSTEM:

7.1	Species:	Rat
7.2	Strain:	CD® (Virus Antibody Free)
7.3	Sex(s)/Number:	100 virgin males 100 virgin females - received approximately 14 days after the males
7.4	Age of Animals:	60 - 70 days old at randomization (assigned to study)
7.5	Body Weight:	Approximately 275 - 350 g (males) and 200 - 250 g (females) at randomization (assigned to study)
7.6	Source of Animals:	Charles River Breeding Laboratories, Inc. The specific source will be documented in the raw data.

7.7 Justification for Selection of Test System: The CD® rat was selected as the animal model for this study because: (1) the U.S. FDA *Guideline on Detection of Toxicity to Reproduction for Medicinal Products* (1994) requires a rodent species, preferably rats, for preclinical reproductive testing of drugs; (2) this species/strain has a proven sensitivity to a variety of agents and therefore provides a suitable animal model for testing chemicals and drugs for human risk assessment: (3) reliable scientific methods currently exist for performing rat reproduction studies; (4) historical data and experience exist; (5) the CD® rat has been used extensively for reproduction testing; and (6) it was specified by the Sponsor.

7.8 Procedure for Unique Identification of Test System: Each animal will be given a study-unique number as a subcutaneously implanted microchip. This number will also appear on a cage card visible on the front of each cage. The cage card will additionally contain the study number, test article identification, treatment group number, sex and dose level. Cage cards will be color-coded as a function of treatment group. Raw data records and specimens will also be identified by the unique test animal number.

7.9 Housing: The animals will be housed in an AAALAC-accredited facility. Animals will be singly housed (except during mating) in polycarbonate cages with Anderson-bed-a-cob bedding (Heinold, Kankakee, Illinois) in a temperature (65-78°F) and humidity (30-70%) controlled room with a 14 hour light/10 hour dark cycle. The cage size, 840 cm^2 area and 20 cm height, is adequate to house rats at the upper weight range as described in the *Guide for the Care and Use of Laboratory Animals*, DHHS (NIH) No. 86.23. All animals will be routinely transferred to clean cages with fresh bedding once weekly.

7.10 Quarantine Procedure: Animals will be quarantined for approximately 14 days. During the quarantine period, the animals will be observed daily for signs of illness, and all unusual observations will be documented and reported to the Study Director or Clinical

Veterinarian. Animals will be examined during quarantine and approved for use by the Clinical Veterinarian prior to being placed on test. Unless deemed unhealthy (based on general clinical observations), all animals will be available for use in the study. If a selected animal appears unhealthy prior to initiation of treatment, it will be replaced by a healthy animal prior to initiation of treatment under the direction of the Study Director. Quarantine release will be documented on the Clinical Veterinarian Log by the veterinarian prior to study initiation.

7.11 Food: Certified Rodent Chow No. 5002 (PMI Feeds, Inc., St. Louis, MO) will be provided *ad libitum* from arrival until termination.

7.12 Water: Tap water from an automatic watering system in which the room distribution lines are flushed daily will be provided *ad libitum* from arrival until termination. The water is not treated with additional chlorine or HCl.

7.13 There are no known contaminants in the feed or water which are expected to influence the study. A copy of the feed certification will be kept with the study records. The results of bimonthly comprehensive chemical analyses of Chicago water are documented in files maintained by Quality Assurance.

7.14 It is not known if the animals will experience pain or distress during the study. Analgesic or anesthetic agents will confound the ability to determine the toxic potential of the test article, and therefore will not be used. If an animal is in severe pain or distress, following consultation with the veterinary staff, it will be euthanized in accordance with standard operating procedures.

8.0 EXPERIMENTAL DESIGN:

8.1 Treatment Groups:

Group	No. of Animals Male	Female	Treatment	Dose Level (mg base/kg/day)	Dose Volume (ml/kg/day)	Dose Conc. (mg base/ml)
1	25	25	Vehicle	0	5	0
2	25	25	WR6026•2HCl	3	5	0.6
3	25	25	WR6026•2HCl	7.5	5	1.5
4	25	25	WR6026•2HCl	18	5	3.6

One hundred ten males and one hundred twenty females will be purchased for the study. The additional females are necessary because a small percentage of females will typically not exhibit healthy vaginal cytology, i.e., they will not cycle properly.

Test article dose levels are selected on the basis of dose range-finding and developmental toxicity studies in female rats (UIC/TRL Study Nos. 170 and 171, respectively) and a

three month toxicity study with a three month recovery period in male and female rats (UIC/TRL Study No. 091). The duration of the male premating dosing period is based on a lack of testicular toxicity in this latter study. The number of animals, 25/sex/dose level, is necessary to result in 16 - 20 litters/group for rodents as recommended in the *ICH Harmonized Tripartite Guideline* (1993).

8.2 Frequency and Route of Administration of Test Article: The test article will be given orally by gavage as follows:

Males: Dosing will be daily for 29 days prior to cohabitation, daily during the 21 day cohabitation period, and daily in the post-cohabitation period until the day prior to necropsy. Accordingly, the dosing period will range from approximately 60 - 70 days. Male necropsies will be scheduled following a discussion with the Sponsor of the female mating and fertility indices (Section 8.8.7)

Females: Dosing will be daily for 15 days prior to cohabitation, daily during cohabitation which may range from 1 to 21 days, and daily during gestation days 0 - 6. Accordingly, the dosing period will range from approximately 23 - 42 days. Sperm-negative females will be dosed until the day prior to sacrifice (Section 8.8.6).

The drug will be given at a dosing volume of 5 ml/kg/day. The control group will receive the vehicle (i.e., the control article) at the same dosing volume. The specific volume to be administered will be adjusted on the basis of the animal's most recent body weight. All animals will receive the control article by gavage for 3 days during week -1 to acclimate them to the dosing procedure.

8.3 Justification of Route(s): The oral route is a convenient and accepted procedure for administering a specific amount of a test article to each animal. It mimics potential human exposure conditions and is specified by the Sponsor.

8.4 Procedure to Control Bias during the Assignment of Animals to Treatment Groups: During week -1, animals judged to be healthy (based on general clinical observations) and meeting acceptable body weight requirements (Section 7.5) will be assigned to the study at random, within sex, using a randomization procedure on the basis of body weight. At the discretion of the Study Director, females that demonstrate acceptable reproductive health (as evidenced by vaginal cytology) but are outside of the acceptable body weight range may be utilized in the study. Similarly, at the discretion of the Study Director, females within the acceptable body weight range but not demonstrating acceptable reproductive health (as evidenced by vaginal cytology) may not be utilized on the study.

8.5 Control Article (Test Article Vehicle): Deionized distilled water.

8.6 Test Article Dosage Form Preparation and Analyses: The test article solutions will be prepared weekly by dissolving the appropriate quantity of test article in the control article. Concentrations will be adjusted for test article purity. Each test article dosing solution will be prepared individually by adding the appropriate amount of WR6026 Dihydrochloride with the required volume of deionized distilled water in a pre-calibrated beaker. The contents will be mixed with an Omni-Mixer homogenizer for at least 2 minutes. Stability data from a previous study (UIC/TRL Study No. 091) indicates that the dosing solutions are stable for at least 12 days. All dosing solutions will be stored at 2 - 8° C. Samples of each set of weekly dosage formulations will be analyzed for test article concentration prior to use. Only samples within 10% of their intended concentrations will be used. All solutions will be allowed to warm to room temperature before gavage administration.

8.7 Breeding: Each female will be cohabitated with a single male from the same treatment group. Within litter cohabitation will not occur because males and females of the same age arrive approximately 14 days apart. Cohabitation will commence after 29 days of dosing in males and after 15 days of dosing in females and will last for 3 weeks, if necessary. Each mating pair will be observed for evidence of mating once daily during cohabitation. Detection of a vaginal copulatory plug or a positive vaginal smear (sperm present) will be considered as evidence of mating. The day on which positive evidence of mating is detected will be designated as gestation day (GD) 0 and will result in separation of the mating pair. The female will be returned to her individual cage.

At the end of the 3 week cohabitation period, sperm-negative females will be separated from their mates and placed in their own cage.

8.8 Frequency of Observations, Test Analyses and Measurements:

8.8.1 Mortality Check: All animals will be observed twice daily, at least six hours apart for moribundity/mortality.

8.8.2 Clinical Signs: All animals will be observed daily for clinical signs of toxicity approximately 1-2 hours after dosing, and in the morning after completion of the dosing period for females. Moribund animals will be sacrificed on that day and necropsies will be performed as described in Section 8.8.8.

8.8.3 Body Weights:

Males: At randomization in week -1 and twice weekly (≈ every 3 - 4 days) during dosing. A final body weight will be recorded on the day of scheduled necropsy.

Females: At randomization in week -1 and twice weekly (≈ every 3 - 4 days) during dosing throughout the cohabitation phase. When positive evidence of mating is detected, body weights will be obtained during dosing on GD0 - 6. and in the postdosing period on GD10, 13, and 16.

8.8.4 Food Consumption:

Males: During week -1 and twice weekly (≈ every 3 - 4 days) except during cohabitation.

Females: During week -1 and twice weekly (≈ every 3 - 4 days) except during cohabitation. When positive evidence of mating is detected, food consumption will be measured during the following intervals: GD0 - 3; 3 - 6; 6 - 10; 10 - 13; and 13 - 16.

8.8.5 Vaginal Cytology: Vaginal washings will be performed in all females to monitor the estrous cycle. Washings will be performed in the quarantine period for approximately 10 days prior to randomization. Washings will be performed daily during the dosing period throughout cohabitation until either evidence of copulation is observed or until termination of the cohabitation period.

8.8.6 Scheduled Necropsy of Females: Females with evidence of mating (i.e., sperm-positive females) will be euthanized by CO_2 asphyxiation and necropsied on presumed GD16. At the discretion of the Study Director, females without evidence of mating (i.e., sperm negative females) will be sacrificed if pregnancy is confirmed (i.e., palpated pregnant). Females without evidence of mating or pregnancy at the end of the cohabitation period will be sacrificed 10 days after the last day of cohabitation. These occurrences will be documented in the raw data.

At necropsy, the thoracic, abdominal and pelvic cavities will be opened and the viscera examined. Any abnormalities will be recorded. All placentas will be grossly examined and any abnormalities will be recorded with the exception of necrotic changes associated with nonviable or resorbing fetuses. The uterus and ovaries will be removed from the body and examined. For sperm-positive females, uteri with microscopic implantations will be opened; and the number of implantation sites, viable and nonviable fetuses*, and early and late resorptions** will be recorded consecutively from the distal end of the left uterine horn to the cervix and then from the distal end of the right uterine horn to the cervix. The *corpora lutea* on each ovary will be counted and the number recorded. For sperm-negative, pregnant females, the number of implantation sites and *corpora lutea* will be recorded and used in the calculation of preimplantation loss and mating and fertility indices. Because the end of the dosing period, i.e., GD6, is unknown, the number of viable and non-viable fetuses and resorption sites in these animals will be recorded and retained with the raw data, but will not be utilized in the statistical analysis.

*A viable fetus is defined as one that has pink, well vascularized tissue; a dark red placenta; and clear, reddish amniotic fluid. A nonviable fetus is defined as one that has white, nonvascularized tissue; a necrotic, green placenta; and cloudy dark amniotic fluid.

**An early resorption is defined as one in which organogenesis is not grossly evident. A late resorption is defined as one in which organogenesis is grossly evident. A fetus with evident autolysis is considered a late resorption.

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Uteri with no macroscopic evidence of implantations will be opened and placed in 10% aqueous ammonium sulfide solution for approximately 10 minutes for detection of early embryolethality. If implantation sites are detected, the number of *corpora lutea* on each ovary will be recorded.

The necropsy procedure will include retention of the uterus and ovaries from all animals and any organs/tissues with gross lesions in 10% neutral buffered formalin for possible histopathologic examination. If any organs/tissues with gross lesions are retained from treated animals, corresponding organs/tissues from a control animal will be retained, when possible, for comparison. Upon issuance of the final report, the Sponsor will provide written directions regarding the disposition of tissues not examined histopathologically.

8.8.7 Scheduled Necropsy of Males: Mating and fertility indices (Section 8.9) will be reviewed by the Study Director and Sponsor's Representative as soon as possible. If apparent adverse effects are noted, the Study Director and Sponsor's Representative will decide if any additional evaluations of the males are required. If no apparent test article related changes are observed, the males will be euthanized by CO_2 asphyxiation and necropsied. The thoracic, abdominal and pelvic cavities will be opened and the viscera examined. Any abnormalities will be recorded. Paired organ weights will be collected from each animal for the testes, epididymides and seminal vesicles. Prostate weights will also be recorded. If observable size, color or consistency differences are noted, the paired organs of the affected animal will be weighed separately. The brain will be weighed for brain to organ weight comparisons.

The necropsy procedure will include retention of both testes in Bouin's fixative, and the left epididymis, prostate, and both seminal vesicles from all animals and any organs/tissues with gross lesions in 10% neutral buffered formalin for possible histopathologic examination. If any organs/tissues with gross lesions are retained from treated animals, corresponding organs/tissues from a control animal will be retained, when possible, for comparison. Upon issuance of the final report, the Sponsor will provide written directions regarding the disposition of tissues not examined histopathologically.

At necropsy, sperm motility will be assessed. Semen samples will be evaluated utilizing the Hamilton Thorne Integrated Visual Optics System (IVOS) 10 Sperm analyzer. The motility sample will be prepared from the vas deferens and will be placed in a suspension medium containing PBS with 1% BSA (Bovine Serum Albumin). After a 3 minute "swim out" period, a 100 µ deep cannula will be inserted into the media and a sample will be drawn up. The cannula will be inserted into the stage and the general examination of the sperm sample will be made on the computer monitor. Based on the results of the motility sample analyses, other parameters including straight-line, curvilinear and path velocities, progressive motility and cross-beat frequency may also be calculated. Sperm samples will be discarded after analysis.

At necropsy, the right epididymis will be trimmed, frozen on dry ice, and temporarily stored at -70°C or less for subsequent sperm counts and sperm

morphology assessment. The epididymal samples will be thawed, and the caudal section will be weighed and minced, and one or two drops will be spread on a slide and stained with Eosin for sperm morphology assessment. The minced caudal epididymal samples will then be homogenized, and a 100 ul sample will be added to a vial containing a florescent dye which stains the DNA in the sperm head. A sample will be loaded into the IVOS and the stained sperm heads will be counted. The results will be reported as total sperm count adjusted for caudal epididymis weight (10^6 sperm/g tissue). Sperm samples will be discarded after analysis.

8.8.8 Unscheduled Deaths: All animals found dead or euthanized *in extremis* during the study and females that deliver early will euthanized by CO2 asphyxiation and grossly examined externally and internally. Body cavities (thoracic, abdominal, and pelvic) will be opened and examined. Uterine contents will be examined and the number of implants will be recorded. The number of *corpora lutea* on each ovary will be noted. Any abnormalities will be recorded. Organs/tissues with gross lesions will be saved in 10% neutral buffered formalin for possible histopathologic examination. Upon issuance of the final report, the Sponsor will provide written directions regarding the disposition of tissues not examined histopathologically.

Uteri with no macroscopic evidence of implants will be opened and placed in 10% aqueous ammonium sulfide solution for approximately 10 minutes for detection of early embryolethality. If implantation sites are detected, the number of *corpora lutea* on each ovary will be recorded.

8.9 Statistical Analyses:

Body weights, body weight gains, calculated daily food consumption, male organ to brain weight ratios, the average number of occurrences of estrus, and the average length of the estrus cycle will be analyzed by one-way analysis of variance. If a significant F ratio is obtained ($p \leq 0.05$), Dunnett's test will be used for pair-wise comparisons to the control group.

Sperm counts, sperm morphology and sperm motility; the numbers of *corpora lutea* (C.L.), implantations, early and late resorptions, viable and nonviable fetuses; and the percent preimplantation loss*, postimplantation loss**, and total implantation loss*** will be compared using the Kruskal-Wallis test. If a significant effect is seen ($p \leq 0.05$), the Mann-Whitney U test will be used for pair-wise comparisons to the control group.

*Preimplantation loss% = [(# C.L. - # implantations)/#C.L.] x 100
**Postimplantation loss% = [(# implantations - # viable fetuses)/# implantations] x 100
***Total implantation loss % = [(#C.L. - # viable fetuses)/#C.L.] x 100

The number of females cycling normally and the following reproductive indices will be compared by Chi-Square analysis. If a significant effect is seen ($p \leq 0.05$), the Fisher's exact probability test will be used for pair-wise comparisons to the control group.

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Mating Index = (No. with evidence of mating/No. cohoused) x 100
Fertility Index = (No. pregnant/No. with evidence of mating) x 100

Sperm-negative pregnant females will be included only in the analysis of the numbers of *corpora lutea* and implantations, the percent preimplantation loss, and the mating and fertility indices.

Other statistical analysis will be conducted as deemed necessary and will be documented in the raw data.

In addition to the written report, summary data tables of parameters and variability will be transmitted to the Sponsor on magnetic media (computer diskette) in "ASCII" form. The transcribed data on disk will no longer be considered GLP compliant.

9.0 RECORDS TO BE MAINTAINED:

All data generated during the conduct of the study, except those that are generated by automated data collection systems, shall be recorded directly, promptly, and accurately in ink in bound books with prenumbered pages or on worksheets that shall be bound during or at the conclusion of the nonclinical laboratory study. All computer and machine output shall be bound during or at the conclusion of the study. All data entries shall be dated on the day of entry and signed or initialed by the person entering the data.

Any changes in entries for whatever reason (e.g., to correct an error or transposition) shall be made so as not to obscure the original entry, shall indicate the reason for such change, and shall be dated and signed or identified at the time of the change. In automated data collection systems, the individual responsible for direct data input shall be identified at the time of data input. Any changes in automated data entries for whatever reason (e.g., to correct an error or transposition) shall be made in such a manner so as not to obscure the original entry, shall indicate the reason for such change, and shall be dated and the responsible individual shall be identified.

Upon completion of the study and submission of the final report, all raw data, documentation, specimens, test article reserves and other materials necessary to reconstruct the study will be stored in the UIC/TRL archives maintained by Quality Assurance.

All changes or revisions, and reasons therefore, to this protocol once it is approved shall be documented, signed by the Study Director and Sponsor, dated and maintained with the protocol.

10.0 REGULATORY REQUIREMENTS:

This study will be performed in compliance with the UIC/TRL Quality Assurance Program designed to conform with FDA Good Laboratory Practice Regulations and EPA Good Laboratory Practice Standards.
Will this study be submitted to a regulatory agency? Yes If so, to which agency(ies)? U.S. Food and Drug Administration

Does the Sponsor Request that test article samples be returned? Possibly; direction will be provided by the Sponsor.
Does the Sponsor request that samples of the test article/carrier mixture(s) be sent to the Sponsor? No

11.0 REFERENCES:

FDA (1994). International Conference on Harmonisation; Guideline on Detection of Toxicity to Reproduction for Medicinal Products. Federal Register, Thursday, 9/22/94.

Gad, S and Weil, CS (1988). Statistics and Experimental Design for Toxicologists, 2nd ed. pp 53-70, 147-176, Telforel Press. Caldwell, NJ.

Hayes, W (1989). Principles and Methods of Toxicology, pp 311-361, Raven press. New York, NY.

ICH (1993). ICH Harmonised Tripartite Guideline: Detection of Toxicity of Reproduction for Medicinal Products. International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use.

U.S. Department of Health and Human Services (1985). Guide for the Care and Use of Laboratory Animals. Prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources. Commission on Life Sciences, National Research Council. Public Health Service, National Institutes of Health, NIH Publications No. 86-23.

12.0 PROTOCOL APPROVAL:

STUDY DIRECTOR: Debra L. Kirchner — 5/9/96
Debra L. Kirchner, Ph.D., D.A.B.T. Date

PRINCIPAL INVESTIGATOR: Barry S. Levine — 5/9/96
Barry S. Levine, D.Sc., D.A.B.T. Date

QUALITY ASSURANCE: Ronald Schoenbeck — 5/9/96
Ronald Schoenbeck Date

SPONSOR APPROVAL: George J. Schieferstein — 5/10/96
George J. Schieferstein, Ph.D. Date
Contracting Officer's
Representative (COR)

COMMENTS FROM THE COR:

UIC The University of Illinois at Chicago

Office of the Vice Chancellor for Research (M/C 672)
310 Administrative Office Building
1737 West Polk Street
Chicago, Illinois 60612-7227
(312) 996-4995

DRAFT

Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-24
Study No.: 218

Manual No: Appendix 1

May 8, 1996

Barry S. Levine
Pharmacology
312 BGRC, M/C 868

Dear Dr. Levine:

The modifications requested in your correspondence of May 6, 1996 pertaining to your approved protocol ACC: #93-077-28: "Oral Fertility and Early Embryonic Developmental Study of WR6026 Dihydrochloride in Rats" have been reviewed in accordance with the Animal Care and Use Policies of the University of Illinois at Chicago. You will be pleased to know that the modifications were approved on May 8, 1996 and consequently the records of Animal Care Committee will be revised to reflect these changes.

Thank you for complying with the Animal Care Policies and Procedures of UIC.

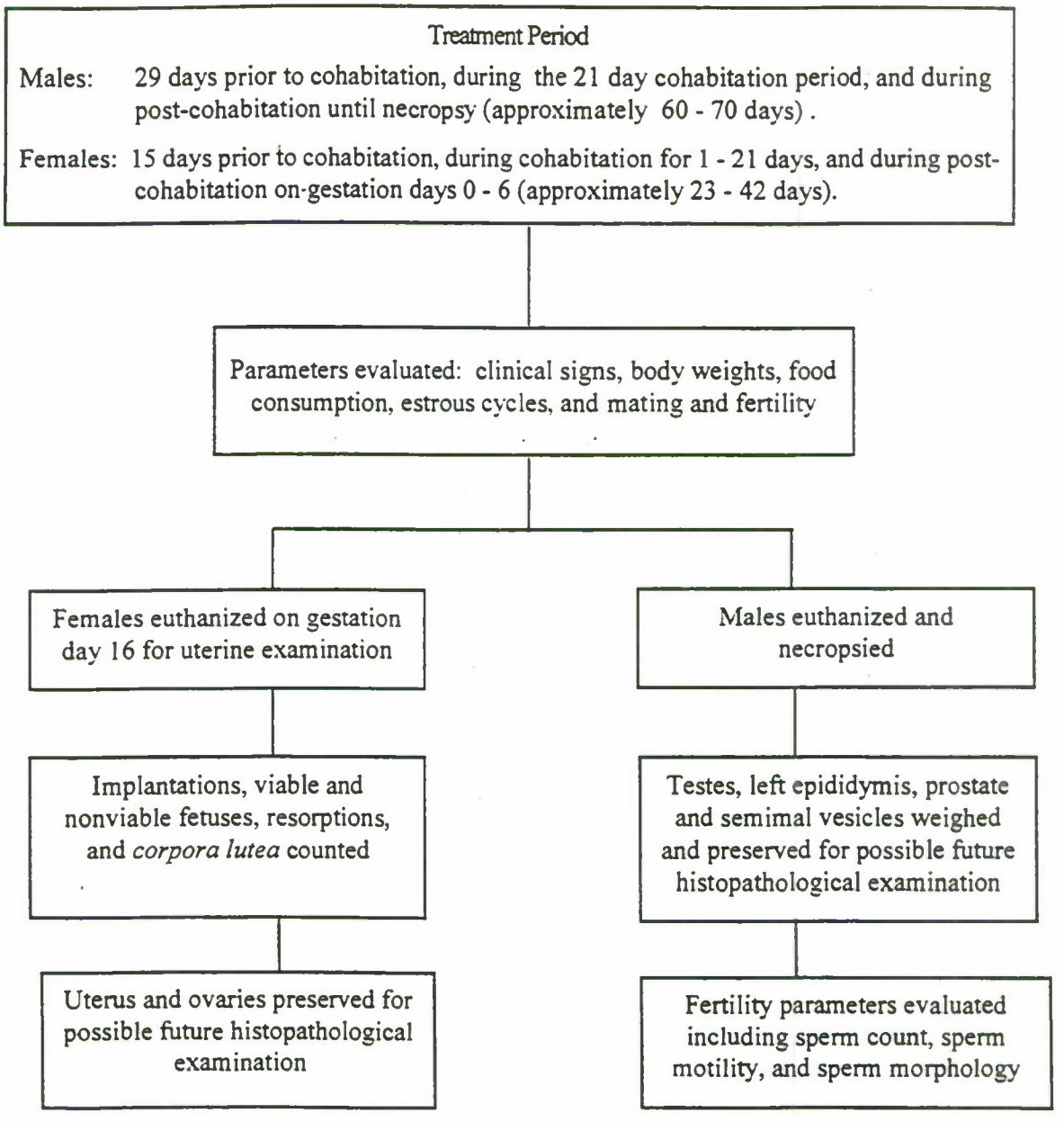
Sincerely yours,

Michael W. Levine, Ph.D.
Chair, Animal Care Committee

MWL:st
xc: BRL

Appendix 2

Experimental Design



DRAFT

PROTOCOL AMENDMENT

Study No.: 218
Title: Oral Fertility and Early Embryonic Development Study of WR6026 Dihydrochloride in Rats

1 Page 1 Section 4.0

Add the following dates:

4.1	Proposed Initiation of Dosing Phase (Males):	07/12/96
4.2	Proposed Completion of In-Life Phase:	09/24/96
4.3	Proposed Study Completion Date (Draft Final Report):	12/24/96

Reason: Dates were not finalized when the protocol was submitted.

APPROVALS:

STUDY DIRECTOR: Debra L. Kirchner — Debra L. Kirchner, Ph.D., D.A.B.T. — 6/11/96 Date

QUALITY ASSURANCE: Ronald Schoenbeck — Ronald Schoenbeck — 6/11/96 Date

SPONSOR APPROVAL: George Schieferstein — George Schieferstein, Ph.D. — 6/12/96 Date

DRAFT

PROTOCOL AMENDMENT

Study No.: 218
Title: Oral Fertility and Early Embryonic Development Study of WR6026 Dihydrochloride in Rats

2. Page 7 Section 8.8.6

In the 1st paragraph, replace the 2nd and 3rd sentences with the following: "At the discretion of the Study Director, females without evidence of mating (i.e., sperm negative females) will be sacrificed if pregnancy is confirmed (i.e., palpated pregnant). Females without evidence of mating or pregnancy at the end of the cohabitation period will be sacrificed 10 days after the last day of cohabitation".

Reason: To clarify when to sacrifice females without evidence of mating (i.e., no presence of sperm in the vaginal washing) but pregnant and females without evidence of either mating or pregnancy.

APPROVALS:

STUDY DIRECTOR: Debra L. Kirchner — Debra L. Kirchner, Ph.D., D.A.B.T. — 9/20/96 Date

QUALITY ASSURANCE: Ronald Schoenbeck — Ronald Schoenbeck — 9/20/96 Date

SPONSOR APPROVAL: George Schieferstein — George Schieferstein, Ph.D. — 9/24/96 Date

DRAFT

PROTOCOL AMENDMENT

Study No.: 218
Title: Oral Fertility and Early Embryonic Development Study of WR6026 Dihydrochloride in Rats

3. Page 2 Section 6.0

Change the Chemistry Specialist from "Thomas Tolhurst, B.S." to "Roohi Gajee, Ph.D."

Reason: To correctly identify the chemistry specialist for the study.

4. Page 9 Section 8.9

A. Change the 1st sentence of the 1st paragraph to read: "Body weights, body weight gains, calculated daily food consumption, male organ to brain weight ratios, the average number of occurrences of estrus, and the average length of the estrus cycle will be analyzed by one-way analysis of variance".

B. Change the 1st line of the 3rd paragraph to read: "The number of females cycling normally and the following reproductive indices will be compared by Chi-Square analysis.

Reason: A. To indicate how estrus data will be analyzed.

B. To indicate how the numbers of females cycling normally will be analyzed.

APPROVALS:

STUDY DIRECTOR: Debra L. Kirchner — 12/17/96
Debra L. Kirchner, Ph.D., D.A.B.T. — Date

QUALITY ASSURANCE: Ronald Schoenbeck — 12/17/96
Ronald Schoenbeck — Date

SPONSOR APPROVAL: _____ _____
George Schieferstein, Ph.D. — Date

APPENDIX H

STUDY DEVIATIONS

ORAL FERTILITY AND EARLY EMBRYONIC DEVELOPMENT TOXICITY STUDY OF WR6026 DIHYDROCHLORIDE IN RATS

Study Deviations*

Deviation Type	Specific Deviation	Effect on Study
Protocol	Female #647 (3 mg base/kg/day) was necropsied on gestation day 17 instead of day 16. Also body weight and food consumption were recorded on gestation day 17 instead of gestation day 16.	None; the animal was dosed for the correct number of days and necropsied during the postdosing period.
Protocol	Male #518 (0 mg base/kg/day) was dosed with 3.6 mg base/ml of test article on day 11 of dosing.	None; individual and summary data for clinical signs, body weights, and food consumption were reviewed and did not reveal any indication of an effect of acute administration of test article.
Protocol	Instead of a 3 minute swim-out time during the collection of sperm motility images, the swim-out time for male #555 (7.5 mg base/kg/day) was 2 minutes; and the swim-out times for male #534 (3 mg base/kg/day) and male #567 (7.5 mg base/kg/day) were 4 and 6 minutes, respectively.	None; these minor alterations did not affect sperm collection or the interpretation of sperm motility parameters.

*The detailed "Deviation Reports" are contained in the raw data which are archived at the Toxicology Research Laboratory, University of Illinois at Chicago, Department of Pharmacology, 1940 W. Taylor St., Chicago, Illinois, 60612.

The above deviations did not affect the integrity of the study.

_____
Debra L. Kirchner, Ph.D., D.A.B.T.

_____
Date